











**National Institute on Aging**

**Annual Report  
of Intramural Research**

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NATIONAL INSTITUTE ON AGING  
INTRAMURAL RESEARCH PROGRAM  
Fiscal Year 1990 Intramural Annual Report

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NATIONAL INSTITUTE ON AGING  
 INTRAMURAL RESEARCH PROGRAM  
 Fiscal Year 1990 Intramural Annual Report

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ANNUAL REPORT OF THE OFFICE OF THE SCIENTIFIC DIRECTOR  
NATIONAL INSTITUTE ON AGING

The Scientific Director, NIA, is responsible for the quality and direction of research conducted by the Intramural Research Program (IRP) which includes nine laboratories and branches in Baltimore and the Laboratory of Neurosciences housed in the NIH Clinical Center. The Office of the Scientific Director is also responsible for central administrative and support functions necessary to the successful operation of the intramural program. Besides the immediate Office of the Director, there is Administrative Services (Administrative Office and Procurement), the Public Information Office, and the intramural Personnel Office.

This year the IRP undertook a major organizational realignment of the Laboratory of Biological Chemistry redirecting programs to concentrate efforts on neurobiology and cell biology. In addition, the Section on Membrane Biology was transferred to the Laboratory of Cardiovascular Science where, under the direction of Dr. Jeffrey Froehlich, this unit will develop a vascular biology initiative to examine the changes in blood vessels that contribute to some 60 percent of deaths in this country.

The Francis Scott Key Medical Center, where the Gerontology Research Center (GRC) is located, is undergoing major development under the auspices of the Johns Hopkins and the Dome Corporation. This will necessitate replacing clinical space formerly utilized for NIA studies and plans were initiated to expand the facilities at the GRC with the creation of a clinical research center next to the existing building. This new facility would be devoted to a clinical research program relevant to disorders associated with aging and the development of intervention strategies to cope with these disorders.

Research progress in the eight laboratories and two branches of the Intramural Research Program and the Epidemiology, Demography and Biometry Program is covered in the following pages, with some of the highlights summarized below.

o Laboratory of Molecular Genetics scientists are looking at one of the gadd (growth arrest and DNA damage inducible) genes, gadd 153, which may help delay cell growth and division to prevent damaged DNA from being replicated. Such cells are transcribed in bacteria and constitute the "SOS" response. While such genes have not been identified in mammalian cells, the gadd153 is a possible candidate whose expression is induced following treatment of cells with agents that damage DNA or inhibit cell growth. Gadd153 may play an important role in preventing the replication of damaged DNA and also have a role in normal cell proliferation, cancer, cell senescence, and aging.

o Research in the Laboratory of Cellular and Molecular Biology examined the effects of age on erythrocyte hypoxic stress associated with the formation and release of superoxide. The work was done both as a function of cellular age and subject age. The human results indicate cellular aging of mature erythrocytes enhances the formation of superoxide which, in turn, escapes the endogenous superoxide dismutase as well as the lysis. No changes were resolved for individual aging even though a younger distribution of cellular ages are found for older subjects. Other studies in rats, in collaboration with Israel's Dr. David Danon, confirmed that older animals possess a younger distribution of cells without producing the expected decrease in the hypoxic stress.





o Investigators in the Laboratory of Biological Chemistry increased their interest in cartilage and bone this year. Dr. C. C. Liang is developing a quantitative model to measure new bone formation. The removal of bone marrow elicits a massive induction of bone formation in the shaft and marrow space of long bones in rodents. This model is expected to provide an ideal system for testing growth factor and cell therapy to restore age-associated deficits in bone.

o AIDS progresses twice as fast in individuals over 40 years of age as it does in younger adults. This year, Dr. William Adler and colleagues in the the Clinical Immunology Section investigated possible reasons for the age-related increase in disease severity and mortality. They studied a clinic population of HIV infected individuals over age 60. The results showed a more rapid loss of T cells in this group. They suspect this is related to the effects of age-associated immunodeficiency in which there is a defect in the generation of functional T cells. In addition, there is less of an antibody response by these individuals to the HIV associated antigens.

o The same scientists studied the types of antibody present in infected persons. There are three major groups of antigens associated with the HIV with each group controlled by either a gag gene, pol gene, or a env gene. The researchers found that, as the disease progresses, antibodies to the gag and pol antigens disappear, while antibody to the env antigens remains constant. This may be due to the lack of functional T cells in the later stages of the illness.

o Researchers in the Laboratory of Clinical Physiology have analyzed diet trends in Baltimore Longitudinal Study of Aging (BLSA) subjects between 1961 and 1987. The study involved 7-day dietary records for 105 community-living men. The age range initially was 17 to 65 years and, in 1981, it was 50 to 88 years. They found that protein consumption in these subjects remained constant over the years but carbohydrate consumption increased. The more striking secular changes were in the type and amount of fat consumed which dropped from 42 percent to 34 percent of kilocalories. There was also a 37 percent decline in cholesterol consumed and a 72 percent increase in the polyunsaturated to saturated fat ratio. These voluntary changes in the diets of community-living men indicate that, at any age, men can make beneficial changes in nutritional intake that can affect health.

o Investigators in the Endocrinology Section, Laboratory of Clinical Physiology completed a study of 28 postmenopausal women on the interaction of age and transdermal estradiol replacement at three different doses. They studied the effects of estrogen before and during progestogen administration on basal growth hormone (GH), GH responses to growth hormone releasing hormone (GHRH), calcium and calcitropic hormone regulation. The results showed that older women remain responsive to the bone conserving influence of estrogen and this effect is not mediated by alterations in plasma calcitonin or increased GH, or insulin-like growth factors (IGF-1). Surprisingly, treatment with transdermal estrogen, unlike oral estrogen, seemed to inhibit the pituitary GH response to GHRH. The researchers concluded that since estrogen did not increase GH or calcitonin, osteoporotic women might benefit from the addition of GH and/or calcitonin therapy to the estrogen therapy plan.

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o The rate of cerebral spinal fluid (CSF) production in healthy older men is reduced to half of that in younger subjects, from 0.4 to 0.2 ml/min, Laboratory of Neurosciences scientists have found. As CSF spaces are larger in elderly persons, a lower production rate indicates that turnover of CSF, which acts as a sink for washing out brain substances, is reduced by more than half in older subjects.

o Inadequate delivery of essential chemotherapeutic drugs to the brain probably accounts for poor therapeutic responses of patients with brain tumors. Drug delivery to such patients, however, can be enhanced by osmotic opening of the blood-brain barrier through intracarotid infusion of a concentrated mannitol solution. This procedure causes morbidity in less than one percent of cases and can significantly prolong survival of patients with primary lymphoma or glioblastomas. Controlled clinical trials are being planned to evaluate the efficacy of the osmotic procedure.

o In another neurosciences study, the alkylating anticancer agent, chlorambucil, was made into a number of esters to increase its lipid solubility and uptake by the brain. The tertiary butyl ester of chlorambucil showed optimum properties. As its half-life in plasma was prolonged, it more rapidly entered the brain than did chlorambucil. Also this ester retained significant alkylating activity. Because this compound shows considerable activity against human tumor cells in vitro, it is being considered for the treatment of human malignancies.

o Laboratory of Behavioral Sciences studies in monkeys have shown a nocturnal hemodynamic pattern characterized by a monotonic fall in heart rate, cardiac output and central venous pressure. There is also a monotonic rise in peripheral resistance. Blood pressure falls early in the evening but does not change overnight, and neither does stroke volume. The investigators suggest this indicates that there is a normal, nocturnal fall in plasma volume in all primates. To determine the cause of the fall in cardiac output, atrial demand pacemakers were implanted in a group of animals. These hemodynamic responses under control conditions were compared to their responses during pacing when heart rate was not allowed to fall overnight. Under these conditions stroke volume fell indicating that the fall in cardiac output was necessary. Events over a 20 day interval of pacing were compared with the control condition--preventing heart rate from falling was associated with a significant rise in left ventricular work and a decline in cardiac performance characteristic of heart failure. The results suggest that one function of sleep may be to allow the heart muscle to rest.

o Laboratory of Personality and Cognition researchers examined the relationship between recognition memory performed on a cued selective recall test with two measures of cognitive status. Subjects were 336 female and male BLSA participants. One view of cognitive aging holds that age declines in memory are due to declines in central processing reports. Recognition memory tasks requiring fewer processing resources have not been thought to be sensitive indicators of age effects. However, impairments in recognition after multiple exposures, such as that provided by cued recall tests, may be sensitive to cognitive impairments not characteristic of normal aging. Many subjects (169) had taken verbal fluency tests an average of 23 years prior to taking the two cognitive status measures given by LPC investigators. The results showed that, indeed, deficits in recognition memory are important and independent indicators of mental status.



o Investigators in the Behavioral Medicine Section, Laboratory of Behavioral Sciences have developed an ambulatory monitor to measure tidal volume and breathing efficiency in people as they go about their daily activities. This device will assist in testing the interaction between naturally occurring daily events and cardiopulmonary function. Baseline studies have already shown that during the day there are frequent falls in breathing frequency below sleep levels that are not compensated for by increases in tidal volume. These episodes are more likely to occur around other people but are not mediated by talking, per se, or by physical activity. This new device should be most helpful in seeking to understand the relationships between cardiovascular and pulmonary function.

o To better delineate age-associated changes in cardiac rhythm and conduction, Laboratory of Cardiovascular Science (LCS) researchers conducted a study to determine the site of the PR interval prolongation associated with aging. Signal average high resolution surface ECGs were performed on 161 clinically healthy Baltimore Longitudinal Study of Aging (BLSA) subjects with normal atrioventricular (AV) conduction. With age, an increase in PR interval was found in both sexes which was localized proximal to the His bundle depolarization, but distal to the P wave inscription. This suggested blockage within the AV junction. A qualitatively similar but more pronounced delay also was noted proximal to the His bundle in seven older men with first degree AV block.

o In more basic research, LCS scientists developed novel single cell techniques to study myocardial contractility, adaptation, and aging of the heart. These techniques permit the simple and reproducible characterization of the length/load-dependent contractile performance of single adult mammalian heart cells, and the simultaneous measurement of the transient change in cytosolic calcium.

o The Laboratory of Neurosciences established a new clinical Unit on Aging and Dementia in the Clinical Center on the Bethesda campus of NIH to facilitate studies on the cause, diagnosis and treatment of Alzheimer's disease. A new Molecular Neurobiology Unit was established at the Gerontology Research Center under the leadership of Dr. Gerald Higgins to help define changes in the aging brain and in disease states.

### Information Office

This year, the IRP Information Office completed the production of the BLSA booklet, Older and Wiser; planned and completed a new exhibit on the Study to recruit collaborators; staffed this exhibit at the annual Gerontological Society of America (GSA) meeting; distributed 400 of the new publication and 20 plus copies of Normal Human Aging in Minneapolis. The exhibit was shown again at Maryland Gerontological meeting in May 1990. The Communications Officer also managed the 1989 GSA pressroom and received an outstanding service award from the same organization for 19 years of service working with media at annual meetings.

Information staff took part in 22 briefings/tours or outside speaking engagements addressing some 200 individuals. Visitors ranged from high school students to scientists or reporters from Brazil, Germany, Japan, Spain, and Singapore. The office helped plan and arrange various aspects of the first Shock Memorial Lecture, including publicity generated in professional journals, newsletters and in local newspapers.

Staff prepared several special report items for submission to Congress for hearings which were later published in the NIA Research Report; also supplied supplemental highlights for possible use in various other hearings this year.



The IO was involved in numerous media interactions--some 200--during the year such as "Good Morning America," (4-minute feature early 1990); French Antenne II TV (interviews with GRC director/staff); Brazilian Globo TV (story aired summer 1990); Cable News Network (story on depression and cancer); all three major Baltimore channels; CBS' "48 Hours;" and, newspapers and magazines, including the Washington Post, Baltimore Sun and Evening Sun, Time, Newsweek (statistics on average changes with aging), Der Stern and GEO (W. Germany magazines), Newsday, Boston Globe.

This office wrote or arranged for two stories, including one this fall, for the Dome Corporation newsletter distributed through FSK, Bayviewpoint. In addition staff produced 12 issues of Geron News, 1 Pages of the Ages, and the CO served as editor and writer for 4 issues of the Maryland Gerontological Association Newsletter and for two MGA conference proceedings.

The Communications Officer managed two Red Cross Blood Drives (110 units); helped publicize and provide gifts for CFC and U.S. Savings Bond campaigns; chaired the Baltimore Federal Executive Board fall 1989 disability awareness conference and emceed the spring FEB Barrier Awareness Day in Baltimore. The IO staff served on a number of committees including the NIH Advisory Committee for Employees with Disabilities; the PHS disabilities committee; the Baltimore FEB Committee for Individuals with Disabilities; and on the board of directors of the Maryland Gerontological Association and the NIH Recreation and Welfare Association.





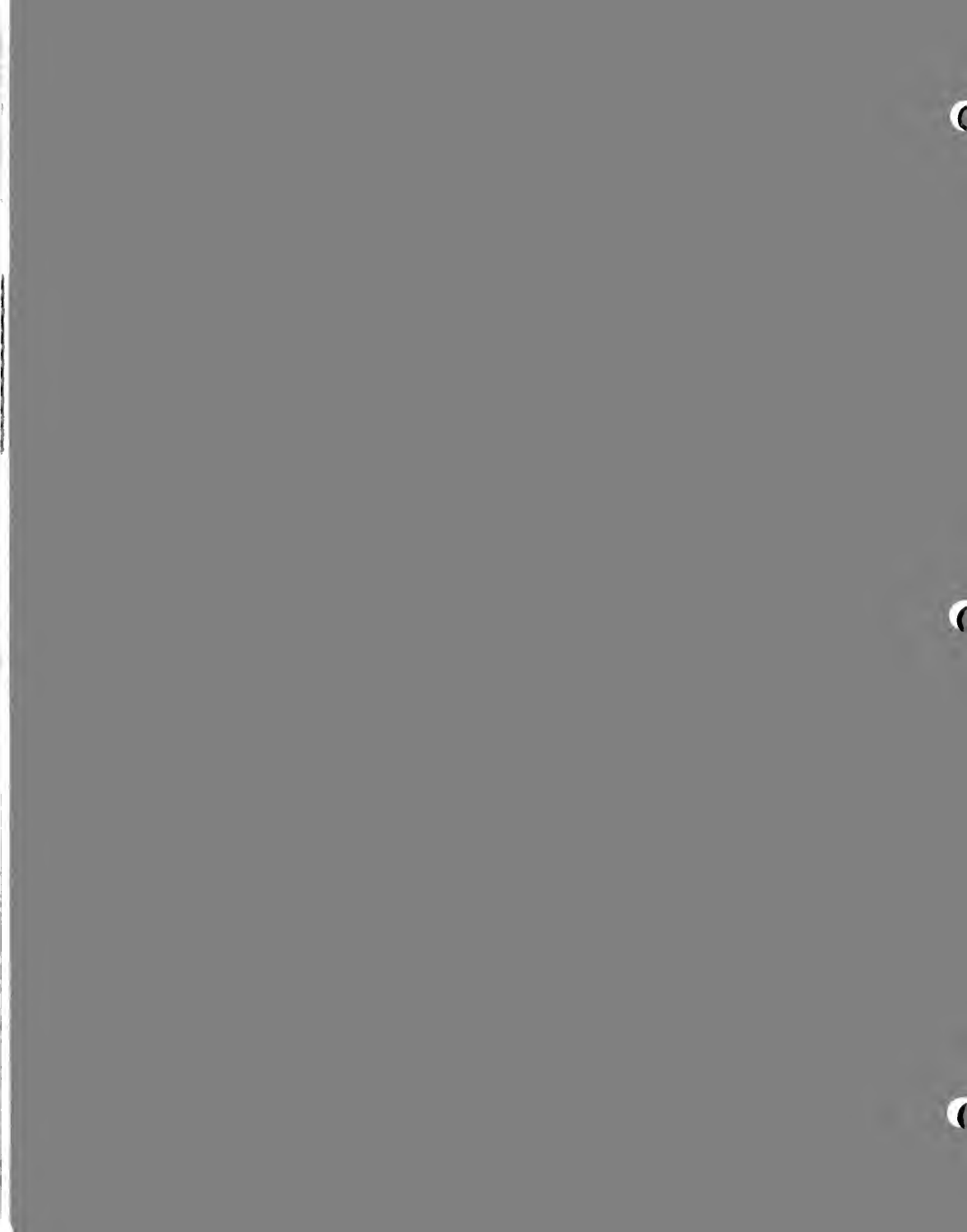
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Annual Report Of The Research Resources Branch  
National Institute on Aging

Technical Development Section

Several major improvements were made to our central computer system. Two high-capacity disk drives (ordered last year) were installed, which in turn allowed us to allocate six smaller drives to individual laboratories for their scratch needs. In addition, two CPU's were added to the system - one in the Laboratory of Clinical Physiology, the other to be used centrally as a SAS batch machine. Software arrived that will increase the capability of the central system to act as a disk/prINTER server for IBM PC's, on the building's network.

The development of general-purpose cards for IBM micro-computers has allowed us to continue replacing obsolete microprocessor-based equipment throughout the GRC. Recently completed were the replacements for equipment used in free-recall and problem solving tests for the Laboratory of Personality and Cognition, and a system to collect rat maze data for the Molecular Physiology and Genetics Section of the Laboratory of Cellular and Molecular Biology. For this same section, a system to collect activity data from caged primates is being developed. A system, which was developed here several years ago to control and monitor monkeys in behavior conditioning experiments in the Laboratory of Behavioral Sciences, was extended to provide the same services for pig studies.

An extensive effort was given to the development of a PC-based system to collect calcium data at moderate rates for the Laboratory of Cardiovascular Sciences. The system includes seven PC's with locally developed and fabricated interface cards - all connected, via ethernet, to a VAX cluster. Additional PC cards that will digitally integrate the 4 micro-second wide fluorescence are currently being developed. In the PC's, menu-driven software allows the experimenter to setup a wide variety of experiments and collect relatively large quantities of data, that are both shipped immediately over the network to the VAX's and stored locally. VAX-based software immediately constructs a graphical summary, which is fed back to the experimenter and places the verified data into a storage structure. Later, the data may be retrieved from the structure and downloaded into popular PC software packages, such as SAS, Lotus 123, and Adobe Illustrator.

Photography and Arts Unit

In addition to the normal production of negatives, slides, prints, and poster materials, the computer graphics system was expanded to include the development of new software for use in the Unit. This new software enables the Unit to produce graphs which closely match almost any type of variation presented to the Unit. Plans are being made to make this software available to any VAX user with the proper hardware. In addition, new hardware has been ordered for the VAX machine room, for use by anyone in the building.

An increased demand for service this past year was matched by an increased capacity from the computer graphics system. A considerable amount of time was saved, not only because some of the work was done by others outside the Unit, but also because the time expended on the computer is far less than the time needed for conventional processes. The Macintosh continues to help the



Unit add to the computer graphic's capability.

### Library Unit

The conversion of some journal volumes into microfilm cartridges has vacated approximately 520 inches of shelf space. Consequently, a large-scale re-arrangement of the library's collection layout became possible, and has been successfully accomplished. Many favorable comments were received from the GRC scientific community, particularly on the relocation of reference books, which has facilitated easier access to needed information. The library support staff received a Special Act Award for their contribution in helping to accomplish this laborious project.

Approximately 500 books were cataloged, of which 63% were added to the library's collection and the remaining 37% were issued directly to the various GRC laboratories and branches. Special emphasis has been focused on the expansion, weeding out, and the updating of reference books. Available data shows that of the library books cataloged, 41% were added to the reference collection.

1,306 interlibrary loan requests were serviced for the GRC scientists, of which 72% were filled by the NIH Library. The range of interlibrary loan requests fluctuated between 47 and 172 per month. Peak times of workload coincided with the summer and winter months, when there were increased number of Stay-In-Schoolers working at the GRC.

Two additional micro-computer, end-user search literature databases have been implemented in the Library Unit. Compared to the monthly update of CDP Medline, which has been in use since 1988, both, Current Contents on diskettes and Reference Updates are updated weekly. Their higher frequency of updates is able to bring more recent, sometimes important, publication information; therefore, both databases have been used as supplemental searching tools for scientific literature.

A new user service was started in fiscal year 1990. An alphabetical listing of new journal issues, received during the week, is made available to users. It serves as a quick guide, assisting researchers in keeping current with their readings of library journals, which are of particular interest to them. The listing was generated by using the library's automated serial control system.

In FY '90, the library purchased an IBM copier and a second microfilm reader/printer to assist in the library's operation.

### Animal Resources Section

A new caging system is now in place, housing the aging Wistar rats. This system provides adequate floor space, uniformity, efficient operation, and expansion. Approximately 2,800 male rats can be added to the colony; thus, reaching a population of 12,800, and resulting in an increase of 20% more aged rats.

In collaboration with, both, in-house and guest scientists, the ARS staff is actively participating in experiments involving a variety of research protocols, ranging from dietary restriction in the Aging Wistar Rat Colony to the behavioral modification of micro-pigs. 380 hours were provided to support



76 aseptic surgical procedures.

5,296 mice and rats were issued from the aging rodent colonies. Care was provided for an average daily population of 11,918 rats, 10,047 mice, 24 dogs, 19 rabbits, 10 non-human primates, and 7 domestic pigs. In addition to these stock animals, approximately 1,084 rats, 6,221 mice, 76 rabbits, 120 hamsters, 4 non-human primates, and 21 pigs were received, housed, and cared for by the ARS.

The entire ARS staff received special achievement awards for their success in accomplishing the plan that maintained our accreditation with AAALAC for the 13th consecutive year. Six ARS employees achieved outstanding EPMS ratings and eight ARS employees achieved excellent EPMS ratings for 1989. For their efforts, each of these employees received individual cash awards.

#### Instrument Design and Fabrication Section

In the past year, along with the many 30 minute to 2 hour construction and repair jobs, the section designed, fabricated, and installed equipment; e.g., installation of a safe work area and a containment hood for investigators working with radioactive materials, constant temperature hand-warming chambers, a video camera positioning device for a mouse maze, lens holders for beam control laser equipment, and a constant monitoring system for use in the swine area.

Due to the re-organization of the various GRC laboratories, the staff of the IDFS have helped dismantle old labs and set up new ones. Everytime this procedure occurred, the IDFS had to relocate wiring for computer terminals. This detailed process was very intricate and time consuming. Various other projects were successfully completed. One IDFS employee achieved an outstanding EPMS rating and four IDFS employees achieved excellent EPMS ratings for 1989. For their efforts, these employees received individual cash awards.





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ANNUAL REPORT OF THE LONGITUDINAL STUDIES BRANCH  
NATIONAL INSTITUTE ON AGING

Nathan W. Shock, Ph.D., the founder of the Baltimore Longitudinal Study of Aging (BLSA) died on November 14, 1989. Recognized as the founder of modern gerontology, Dr. Shock counted the BLSA as one of his major career accomplishments. When the Longitudinal Studies Branch (LSB) was established in FY 1986, Dr. Shock chose the Branch as the organizational unit at the Gerontology Research Center to which he was assigned as NIH Scientist Emeritus. He was active in the Branch as a source of information and most of all inspiration. He actively collaborated on the analyses of longitudinal data. One of his last works was a manuscript describing the accomplishments of the BLSA prepared for Scientific American. The manuscript was revised after Dr. Shock's death by Dr. George Baker and the BLSA director, aided by other senior staff, and is expected to be published in the fall or winter of 1990. We miss Dr. Shock and will cherish his memory.

During the reporting period, the BLSA has been criticized for having a lack of women participants and reports of research about aging and women. It has also been criticized for lack of minority representation in the population of participants. The cornerstone of the criticism about women is the citation of the title of an earlier secondary report about the BLSA entitled "Normal Human Aging". The book written in 1981 and published in 1984 focused on the then available longitudinal studies which of necessity summarized data available on male participants inasmuch as the first women participants joined the study in 1978. The primary reports about BLSA research are in the over 400 articles published since the study began in 1958. Over half of those have been published since 1982 and over 90 include women in the analyses. Specific findings about gender differences in patterns of health and aging are being published with increasing frequency and several descriptions of current findings are summarized in the Annual Reports of this Branch as well as those of LBS, LCP, LCS, and LPC.

Black male and female participants in the BLSA constitute about 5% of the participants; no other minority group is represented in significant numbers. The black participants, like their caucasian counterparts, represent a relatively narrow band of the socioeconomic spectrum of the country; as a group they are highly educated, hold professional and managerial jobs, are health conscious, and desirous of making a contribution to the scientific study of aging through their contribution of time as research participants. All participants in the study are self selected, recruited mostly by existing participants. New participants are admitted to the BLSA from a waiting list of over 1000 adults according to age and gender in such a way as to insure equal numbers of men and women in all age groups who have had a minimum of 12 years of observation in the study (6 years for participants entering the study in their 80s).



The position of the Director of the BLSA with regard to minority representation in the BLSA is that the most important questions relating the interplay of aging and disease that are appropriately addressed in a longitudinal study reflect the operation of socioeconomic factors affecting differences in life style, diet, occupation, educational attainment, and patterns of access to and utilization of health care services. To mount an appropriate research effort using minority populations as part of the BLSA would require the addition of both minority and caucasian participants representing a wide range of socioeconomic status. The resources required would most likely include some compensation for at least some of the participants, particularly hourly wage earners for time lost from work. The present BLSA participants are not compensated for their time nor reimbursed for travel expenses. A subcommittee of the BLSA Steering Committee studied the use of the BLSA in minority aging in FY 1990. To date a consensus has not been reached relative to the proper role of the BLSA in studies of minority aging. We are taking steps to increase the use of the BLSA and the scientists who work with it in the training of young scientists representing minority groups and are seeking to include the question of the most useful role of longitudinal studies such as the BLSA as part of the deliberations of the NIA Task Group on minority aging.

The FY1990 Annual Report consists of 18 project reports. The first four describe the overall goals and direction of the BLSA, population dynamics, management of the data, and the clinical health evaluation that is provided to all participants on every visit. The remaining 14 projects describe the research activities of the LSB staff carried out in connection with the BLSA and related studies.

The scientific mandate of the LSB with respect to the BLSA has three parts. The first is to provide clear scientific leadership and direction to the BLSA--setting directions for the future of the BLSA that accommodate the scientific interests of the many investigators who use the BLSA, but at the same time transcend their specific interests in order to understand the aging process and the process of aging. The second is to take advantage of the long legacy of descriptive data collected in the BLSA over the past 32 years. A number of the longitudinal projects were unanalyzed and entrusted to the LSB at the time of its creation in FY 1996. As is evident in the following project reports, the subject matter of the unanalyzed projects is very broad. They are now being analyzed and longitudinal results from a number of studies are either published or in press. Each project is being examined to determine if changes are needed to bring the ongoing activity up to current standards; if the scientific activity is worth continuing; and if new scientific directions for the activity are required. The third part of the mandate is to manage and operate the BLSA in a manner that fully implements the scientific goals of the Study--managing the population dynamics, the data bank, and the operations of the Study that keep it running properly. The Annual Report speaks to each of three parts of the mandate.

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Overall leadership and direction. Every scientific peer review of the BLSA including the most recent by the Board of Scientific Counselors in 1986 has stressed the need to provide improved scientific direction to the BLSA. The pervasiveness of this recommendation has its roots in two observations. One is a perceived lack of connections across the ongoing research activities. The second is the lack of depth of the scientific activities. Virtually all of the ongoing studies are descriptive with little provision for examining the mechanisms underlying the measured age related phenomena. Constraints in all longitudinal studies include turnover in scientific personnel, research volunteers, and continual, rapid changes in scientific knowledge. Accordingly, longitudinal studies are not usually the setting to incorporate the latest techniques or to address the immediate 'cutting edge' questions. With foresight, longitudinal studies can be selected now that will answer important questions in the future. The vision to do so derives from a detailed examination of each existing project as to its future potential. The essential operational ingredient to providing excellent leadership and direction to the BLSA is the management of change.

During the reporting period, several steps were taken to chart future directions of the BLSA. Discussion of two cross disciplinary initiatives were begun that represent new directions for the BLSA. One is a study of age changes in strength that renews and improves the descriptive analysis of muscular strength and endurance in the BLSA and provides for a parallel intervention study. The latter allows for an examination of mechanisms underlying age related losses in strength; it was prepared by a multidisciplinary working group organized in the LSB. The second is an effort by BLSA Steering Committee members to plan a multidisciplinary project built around age changes in major control systems, e.g., the endocrine, immune, and central nervous systems. The latter initiative is in a development stage at present. Both initiatives speak to criticisms of the BLSA, i.e., the lack of cross disciplinary projects and the failure to plan studies that go beyond a descriptive level.

Rapid advances in molecular and cellular biology have created new research opportunities for uses of biological specimens from BLSA participants. Within the GRC, the Scientific Director has established a committee to consider the establishment of a DNA bank and the future scientific uses of stored blood and urine products. The potential future uses of skin biopsies is being considered in collaboration with the committee that advises the NIA on the uses of cell lines, many of which come from the BLSA.

We are exploring the possibilities of future uses of mortality information and autopsy protocols in the BLSA. The first descriptive paper of the mortality experience in the BLSA was submitted for publication and the newly implemented mortality data base is fully operational. Vigorous efforts are underway to develop special protocols for the BLSA autopsy program, although progress to date has been slow. Our ability to describe the generality of the results of the BLSA has been increased considerably by the completion of the follow-up study of the inactive participants.





At a more conceptual level, the traditional approaches to defining aging in the BLSA is being reexamined. The model of aging that has guided almost all of the analyses of data from the BLSA is one in which normal is defined by average values in a subsample which has been purged of individuals whose data are believed to be unrepresentative of normal, leaving estimates of aging based on 'squeaky clean' data, to use the phrase of Dr. Shock. According to this approach, the major descriptive task is complete after the purging operation, assuming that the question of generalizability is dealt with satisfactorily--aging defined by default. While such a descriptive effort is necessary in the scientific study of aging it is not sufficient. The natural history of aging includes insults by and adaptation to disease and environmental events which are intertwined with aging. The description of aging must include these factors. Central to this concept is our belief that aging processes set the stage for some age related diseases even though they may not be pathological themselves. At the level of the BLSA, it is expected that operational meaning to the concept of the interdependence between aging and disease will be sought by modifications in the clinical evaluation. Much of the reasoning behind these beliefs is spelled out in an article published by LSB staff in the July 1990 issue of the Journal of Gerontology, "Next steps in studying health disease relationships in longitudinal studies of aging."

One of the characteristics of published data from the BLSA is the large variability both between and within persons in age related changes in function. Statistical methods are being developed that will better examine this variability than is available with current techniques. Current examples of such statistical research in the LSB include exploring the relationship between disease and aging as a determiner of the variability between persons and the stability over several serial measurements of variables used to define risk factors.

BLSA legacy. The second part of the LSB mandate concerns the scientific use and usefulness of the BLSA legacy--the collection of longitudinal projects that have been initiated at various times in the history of the BLSA, but have not been analyzed. In most but not all of these projects, data collection is continuing. Aggressive efforts to get the data analyzed and reported, to bring the quality of the research activity up to contemporary scientific standards when needed, and to set new directions for the research have been in place since FY 1986. During the reporting period, analyses of six previously unanalyzed projects have been initiated: simple and disjunctive reaction time; reciprocal manual movement speed; nerve conduction velocity; the smoking history; alcohol use history; and the health evaluations of the female BLSA participants. Data from the first, fourth and sixth of these areas will be presented for the first time at national meetings in the fall of 1990.

Highlights. The research activities of the LSB staff and their collaborators are described in 14 project reports that are organized into three broad groupings: sensation and perception in aging; health/disease relationships in aging; and statistical research in longitudinal studies. Some highlights are presented below; in each area the highlights will focus first on future directions and second on the BLSA legacy.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00015-32 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Baltimore Longitudinal Study of Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J. L. Fozard	Chief, LSB & Asso. Scientific Director	BLSA, OSD, NIA
L. J. Brant	Mathematical Statistician	LSB, NIA
E. J. Metter	Medical Officer	LSB, NIA
N. W. Shock	Scientist Emeritus	NIA
C. Morrell	IPA, Loyola College, Baltimore, Statistics	
J. Pearson	IRTA Fellow	LSB, NIA
B. Hiscock	Program Analyst	LSB, NIA
Other Investigators: See next page		

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center (FSKMC); National Institute of Dental Research (NIDR);

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.15

## PROFESSIONAL:

.80

## OTHER:

1.35

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Baltimore Longitudinal Study of Aging (BLSA), the NIA's major research program on human aging, has been conducted at the Gerontology Research Center since 1958. The overall scientific goals of the BLSA are:

To identify differences among individuals of different ages and changes that occur in the serial observations of these individuals with the passage of time; to determine the relative contribution of aging, disease processes, cohort effects and secular effects in producing observed differences and changes; and to establish the degree of interrelation and/or interaction among these factors.

To expand scientific understanding about predictors and risk factors for specific diseases and for other end points related to successes and failures of adaptation to aging processes.

Scientists working with BLSA are assigned to 11 sections of 7 laboratories in addition to the LSB. The Chief, LSB is the Director of the BLSA and LSB staff administer and manage the BLSA as well as conduct research with it.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00624-01 LSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

BLSA Population Dynamics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

J. L. Fozard	Chief, & Assoc. Scientific Director	BLSA, LSB, NIA
L. J. Brant	Mathematical Statistician	LSB, NIA
E. J. Metter	Medical Officer	LSB, NIA
C. Morrell	IPA	Loyola
B. S. Hiscock	Program Analyst	LSB, NIA
C. Bacal	Physician Assistant	FSKMC
C. Dent	Supervisory Biologist	LSB, NIA
C. Willey	Secretary to Assoc. Scientific Director, BLSA	LSB, NIA

COOPERATING UNITS (If any)

Johns Hopkins Medical Institutions (JHMI), Loyola College

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.67

PROFESSIONAL:

.57

OTHER:

2.10

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The total number of participants ever studied in the Baltimore Longitudinal Study of Aging (BLSA) reached 2018: 1106 active participants, 415 inactive, and 497 deceased. BLSA Population Dynamics refers to optimal management and scientific description of the total population.

We are close to reaching our sample size goal set in 1987, and based on past attrition. This sample size provides for 12-year follow-up of 30 men and 30 women in each age decade from 20 through 70, and 6-year follow-up of those in their 80's. We are examining key differences in the demographics of the BLSA men and women who joined the Study since 1978, and comparing the sample demographically to national statistics and other longitudinal studies.

In a recently submitted manuscript, mortality patterns in the BLSA males were described and compared with those of U.S. white males regarding leading causes of death, death rates, and longevity. We will take part in a symposium at the 1990 Gerontological Society of America meetings with scientists from the Duke, Framingham, and Boston V.A. longitudinal studies to compare mortality patterns in our four studies and the U.S.

The rate of autopsies performed as part of the BLSA autopsy program, begun in 1986, has increased. Almost half of the 17 autopsies performed under this program have been done in 1990.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00625-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Baltimore Longitudinal Study of Aging Data Management

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. A. Shefrin (a) Computer Scientist LSB, NIA

Others: C. B. Eames Ass't Data Base Mgr. LSB, NIA  
N. S. Gittings Programmer/Analyst LSB, NIA  
G. J. Hammen Computer Technician LSB, NIA  
S. A. Pegram Computer Technician LSB, NIA

(a) currently in training

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.70

## PROFESSIONAL:

.80

## OTHER:

1.90

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Data Management work group is responsible for the storage of both paper and computer records generated by the BLSA. They perform the data entry of medical records and manage the data entry of many of the other data collected by BLSA internal investigators, and outside collaborators. Staff members manage the BLSA Computer System and its data base. They support both the administration of the BLSA as well as its scientific activities. Their functions include data extraction, processing and analysis; consultation; training; hardware and software maintenance; and software development.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00622-02 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA: Clinical Health Evaluation

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	J.L. Fozard	Chief	LSB, NIA
	B. Hiscock	Program Analyst	LSB, NIA
	J. Fleg	Staff Cardiologist	LCS, NIA
	D. Kramer	Nurse Practitioner	FSKMC
	D. Brinkley	Nurse Practitioner	FSKMC
	A. Rosenberg	Nurse Practitioner	FSKMC
	C. Kopac	Nurse Practitioner	FSKMC
	C. Bacal	Physician Assistant	FSKMC

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center (FSKMC)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.45

## PROFESSIONAL:

.85

## OTHER:

.60

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

In the past year a number of changes have occurred in the health evaluation during the first morning for the participants in the BLSA. A new way of listing clinical diagnoses has been implemented that separates active diagnoses from inactive diagnoses and from laboratory and clinical observations. Several different medication forms were tested, and now we have implemented a new medication protocol that improves the accuracy of the medication lists, and assigns medications to specific categories that will improve the research quality of the data set. A major effort was made to complete the development of a new set of health questionnaires. These are now been tested, and will be implemented as of October 1, 1990. A revised physical examination protocol has been completed, and will be ready for testing in early November 1990. It is hoped that the physical examination will be implemented on January 1, 1991.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00626-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Changes in Visual Functioning

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fozard	Chief	LSB, NIA
	E. J. Metter	Medical Officer, BLSA	LSB, NIA
	N. S. Gittings	Computer Programmer	LSB, NIA
	C. L. Dent	Testing Manager	LSB, NIA
	F. Schieber	Guest Researcher	Oakland University
	D. W. Kline	Guest Researcher	University of Calgary
	T. S. Kline	Guest Researcher	University of Calgary

## COOPERATING UNITS (if any)

Oakland University, University of Calgary

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.26

## PROFESSIONAL:

.16

## OTHER:

.10

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Laboratory based and questionnaire assessments of visual functioning in relationship to aging are being carried out in male and female participants in the BLSA. Contrast sensitivity measured by the ability to detect alternating dark and light bars of varying widths, was measured in over 250 BLSA volunteers. Self-reported difficulties in visual functioning were being measured in all BLSA participants. Increasing age is associated with greater difficulty in "seeing" unexpected vehicles, estimating vehicle speed, seeing dim displays, annoyance by glare and reading road signs. Analysis of existing data continues and a review of modifiable environmental factors that are involved in age related declines in visual function was prepared.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00627-01 LSB

PERIOD COVERED

October 1, 1987 to October 1, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Risk Factors for Age Related Ocular Changes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Sheila West	Guest Researcher	LSB NIA
Other:	Neil Bressler	Asst. Prof., Wilmer Institute	JHU
	Hugh Taylor	Prof., Wilmer Institute	JHU
	Stuart Fine	Prof., Wilmer Institute	JHU
	Evan Farmer	Prof., Dermatopathology	JHU
	James L. Fozard	Chief	LSB NIA

COOPERATING UNITS (if any)

Wilmer Institute (Johns Hopkins University School of Medicine)  
National Eye Institute

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION NIA, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

.21

PROFESSIONAL:

.21

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to determine risk factors for the leading causes of blindness in the United States, age-related macular degeneration, cataracts, and glaucoma. Specifically, the study is examining the association of dermal elastotic degeneration and anti-oxident vitamin status with age-related macular degeneration; the association of vitamin intake and cigarette smoking with cataract; and the longitudinal relationship between intraocular pressure and systemic blood pressure. A total of 719 participants age 40 and older with at least one visit prior to the ocular study were eligible, of whom 96% had macular and lens photographs to assess ocular status. Data are currently being analyzed for risk factors.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00628-01 LSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and Auditory Characteristics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	Sandra Gordon-Salant	Guest Researcher	LSB NIA
Other:	James L. Fozard	Chief	LSB NIA
	E. Jeffrey Metter	BLSA Medical Officer	LSB NIA
	Larry J. Brant	Mathematical Statistician	LSB NIA

COOPERATING UNITS (if any)

University of Maryland

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.77

PROFESSIONAL:

.27

OTHER:

.50

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project aims to combine assessment of hearing abilities among subjects of different ages over time, together with information from their communication and health histories. Medical and cognitive data collected from subjects in the longitudinal study will be examined with respect to the audiologic and case history data. Specifically, the objectives of this project are: A) To study the contribution of medical, genetic, dietary and social factors to age-related auditory dysfunction; B) To determine to what extent age, independent of other etiologic factors, causes a deterioration in hearing abilities; C) To identify specific hearing abilities and auditory system functions that exhibit the greatest age-related decrements, and to determine whether these changes are associated with other age-related changes in the individual; D) To study the influence of age-related changes in cognition to decrements in speech understanding ability; and E) To examine age-associated changes in self-perceived hearing handicap in relation to hearing sensitivity and speech recognition ability.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00629-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA Men: Distribution of Diseases

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	J.L. Fozard	Chief	LSB, NIA
	L.J. Brant	Statistician	LSB, NIA
	J.D. Pearson	IRTA Fellow	LSB, NIA
	G. Baker	Guest Investigator	LSB, NIA
	R. Kriner	Consultant	AARP

## COOPERATING UNITS (If any)

American Association of Retired Persons (AARP)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.07

## PROFESSIONAL:

.07

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In the past year, we have expanded studies on the clinical evaluation of health-disease relationships in the BLSA men. The goal is to understand the changing health status of an aging individual, and how disease interacts with normal aging to affect health. Until now, we have focused on the appearance of specific diagnoses without regard to the severity of the disorder. For the future, we must refine these definitions so that severity is considered. This will result in a more complete multidimensional functional definition of health. Current projects include (1) analysis of the distribution of disease in relation to age, and (2) analysis of the implications of elevated total white blood counts (WBC) by age on the distribution of diseases by age. At different ages a chronic elevation of WBC has different diagnostic implications.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00630-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA Women: Distribution of Diseases

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	K. McCormick	Nurse-Director	LBS, NIA
	D. Kramer	Nurse Practitioner	FSKMC
	D. Brinkley	Nurse Practitioner	FSKMC
	A. Rosenberg	Nurse Practitioner	FSKMC
	C. Kopac	Nurse Practitioner	FSKMC
	C. Bacal	Physician Assistant	FSKMC

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center (FSKMC)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: .16

PROFESSIONAL: .16

OTHER: 0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Aging women experience life changes differently than men. Data from the BLSA have been analyzed to compare and to contrast: 1) male and female issues of longitudinal study demographics, 2) frequency of common diseases among men and women; 3) drug treatment of these common diseases, 4) the differential effects on biological markers of natural versus artificially induced menopause, and 5) the prevalence of urinary stress incontinence in women and its relationship to the aging process.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00631-01 LSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA Men: Bias Issues

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	J.L. Fozard	Chief	LSB, NIA
	L.J. Brant	Statistician	LSB, NIA
	J.D. Pearson	IRTA Fellow	LSB, NIA
	B.S. Hiscock	Program Analyst	LSB, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.22

PROFESSIONAL:

.19

OTHER:

.03

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In epidemiological and longitudinal studies, there are specific measurement and selection biases that can affect conclusions regarding the relationships between disease and aging. Previously, we presented preliminary studies examining the consistency and reliability of responses to the clinical health evaluation, and selection bias as it related to cardiovascular diseases. During this reporting period, we expanded the studies to include all BLSA men. In addition, we examined the comparability of healthy younger and older men when used for cross-sectional studies. Three studies will be reported: (1) reliability of responses in the health evaluation, (2) selection bias in prevalence of disease based on age at entry, and (3) comparability of healthy sixty and eighty year old men.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00632-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA Men: Perceived Health Status

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	J.L. Fozard	Chief	LSB, NIA
	B.S. Hiscock	Program Analyst	LSB, NIA
	J.D. Pearson	IRTA Fellow	LSB, NIA
	K. Elliott	Guest Investigator	GMU
	P. Knight	Guest Investigator	GMU
	D. Hiebert	Guest Investigator	GMU

## COOPERATING UNITS (if any)

George Mason University (GMU)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.22

## PROFESSIONAL:

.18

## OTHER:

.04

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The project analyzed the association between health complaints as estimated by the Cornell Medical Index (CMI) and self perceived health. The analysis was done in two parts: (1) a master's degree thesis that explored the responses in men over 55 years of age in a case-control study, and (2) a general study of BLSA men, with a focus on how well self-perceived health predicted responses on the CMI, and how well the CMI predicted self perceived health. A moderate degree of predictability was observed, with cardiovascular/hypertension questions being the best predictors of self perceived health.

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LCMB-IRP-NIA

LCP-IRP-NIA

LBS-IRP-NIA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00633-01 LSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health and Disease Status in the BLSA: The Prostate Gland

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.J. Metter	Medical Officer	LSB, NIA
	J.L. Fozard	Chief	LSB, NIA
	R. Andres	Chief	LCP, NIA
	H.A. Guess	Guest Researcher	LSB, NIA
	H.M. Arrighi	Guest Researcher	LSB, NIA
	B. Carter	Asst. Professor	JHU
	P. Walsh	Chief, Dept. Urology	FSKMC

COOPERATING UNITS (if any)

Merck, Sharp & Dome (MSD), University of North Carolina (UNC),  
Johns Hopkins University (JHU), Francis Scott Key Medical Center (FSKMC)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.09

PROFESSIONAL:

.09

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

In the past year progress has been made in characterizing the distribution of BPH in the BLSA men. This has resulted in one published report and one study in press. Of 1057 men whose records were examined 527 were found to have a clinical diagnosis of BPH. By age 80-84, the age specific incidence per year was 159.0 per thousand for BPH, and 36.8 per thousand for prostatectomy. A multivariate analysis determined which questions relative to the prostate from a general clinical evaluation were most useful in predicting subsequent prostatectomy. A second study examined how well the cumulative prevalence of benign prostatic hypertrophy compared to the prevalence of BPH reported at autopsy. A separate study is in progress to examine prostate specific antigen as a marker of prostatic cancer with collaborators from Johns Hopkins University.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00634-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Changes in Pulmonary Function

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: Melvyn S. Tockman	Guest Researcher	LSB NIA
Other: Bernice H. Cohen	Guest Researcher	LSB NIA
James L. Fozard	Chief	LSB NIA
E. Jeffrey Metter	BLSA Medical Officer	LSB NIA
Robert Wise	Associate Prof. of Medicine	JHU

## COOPERATING UNITS (if any)

The Johns Hopkins University School of Hygiene, The Johns Hopkins University School of Medicine, Francis Scott Key Medical Center (Dept. of Medicine)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.16

## PROFESSIONAL:

.31

## OTHER:

.85

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Six initiatives are pursued by the program in pulmonary aging at the GRC-BLSA. These initiatives: a) describe the normal longitudinal decline in pulmonary function; b) relate accelerated decline in pulmonary function to clinical indices of Ischemic Heart Disease (IHD) and thallium perfusion scans; c) evaluate the contribution of bronchial reactivity and d) micronutrient levels to rates of decline of ventilatory function; e) examine the contribution of oxygen delivery to the mechanism associating impaired ventilation with IHD and diminished function. A sixth project conducts cross-population pulmonary function comparisons of the BLSA with the Senior Athlete and Teaching-Nursing Home populations.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00635-01 LSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Changes in Response Speed and Nerve Conduction.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.L. Fozard	Chief	LSB, NIA
	E.J. Metter	Medical Officer	LSB, NIA
	J.M. Wood	Psychologist	LSB, NIA
	M. Vercruyssen	Consultant	USC

COOPERATING UNITS (if any)

University of Southern California (USC)

LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

SECTION

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

.47

PROFESSIONAL:

.17

OTHER:

.30

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Two measures of age related slowing of behavior are being analyzed to describe the age related differences as well as age changes. The age related changes in reaction time were not as robust as the cross-sectional differences suggesting that other factors than age are responsible for part of the age declines observed. Nerve conduction velocity decreased with older age with the age difference becoming apparent around age fifty.

LMG-IRP-NIA

LCMB-IRP-NIA

LCP-IRP-NIA

LBS-IRP-NIA

LBS-IRP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00636-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Study of Physical Activities in the BLSA

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	Linda P. Fried	Guest Researcher	LSB NIA
Other:	J.L. Fleg	Cardiologist	LCS NIA
	E. Gundy	Research Asst.	JHU
	J.D. Tobin	Chief, Applied Physiol.	LCP NIA
	J.L. Fozard	Chief	LSB NIA

## COOPERATING UNITS (if any)

Johns Hopkins Medical Institutions

## LAB/BRANCH

Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

GRC, NIA, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.03

## PROFESSIONAL:

0

## OTHER:

.03

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

This study has analyzed data on physical activity patterns in participants in the Baltimore Longitudinal Study of Aging to determine how physical activity levels change as people get older, whether and how they differ between men and women, and whether regular physical activity has increased over the last 15 years. Answers to these questions will help to understand how best to evaluate physical activity levels in older persons compared to younger persons, and in women compared to men. The most valid approach is necessary to determine the association of physical activity to health as people age. In addition, understanding of whether physical activity levels have increased over time is important in understanding the impact of public health campaigns in the U.S. This study has determined that physical activity levels decrease as people get older, and that older adults, both men and women, primarily obtain their physical activity from walking and housework. This information will help to change the questionnaires currently used for assessing physical activity. In the BLSA population, there has been a 21% increase in energy expenditure over a 15 year period. This significant increase indicates a major change in this important health habit.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00637-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Individual Variability in Human Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	L.J. Brant	Mathematical Statistician	LSB, NIA
	J.D. Pearson	IRTA Fellow	LSB, NIA
	C.H. Morrell	IPA	LSB, NIA
Others:	J.L. Fozard	Chief	LSB, NIA
	E.J. Metter	Medical Officer, BLSA	LSB, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.79

## PROFESSIONAL:

.49

## OTHER:

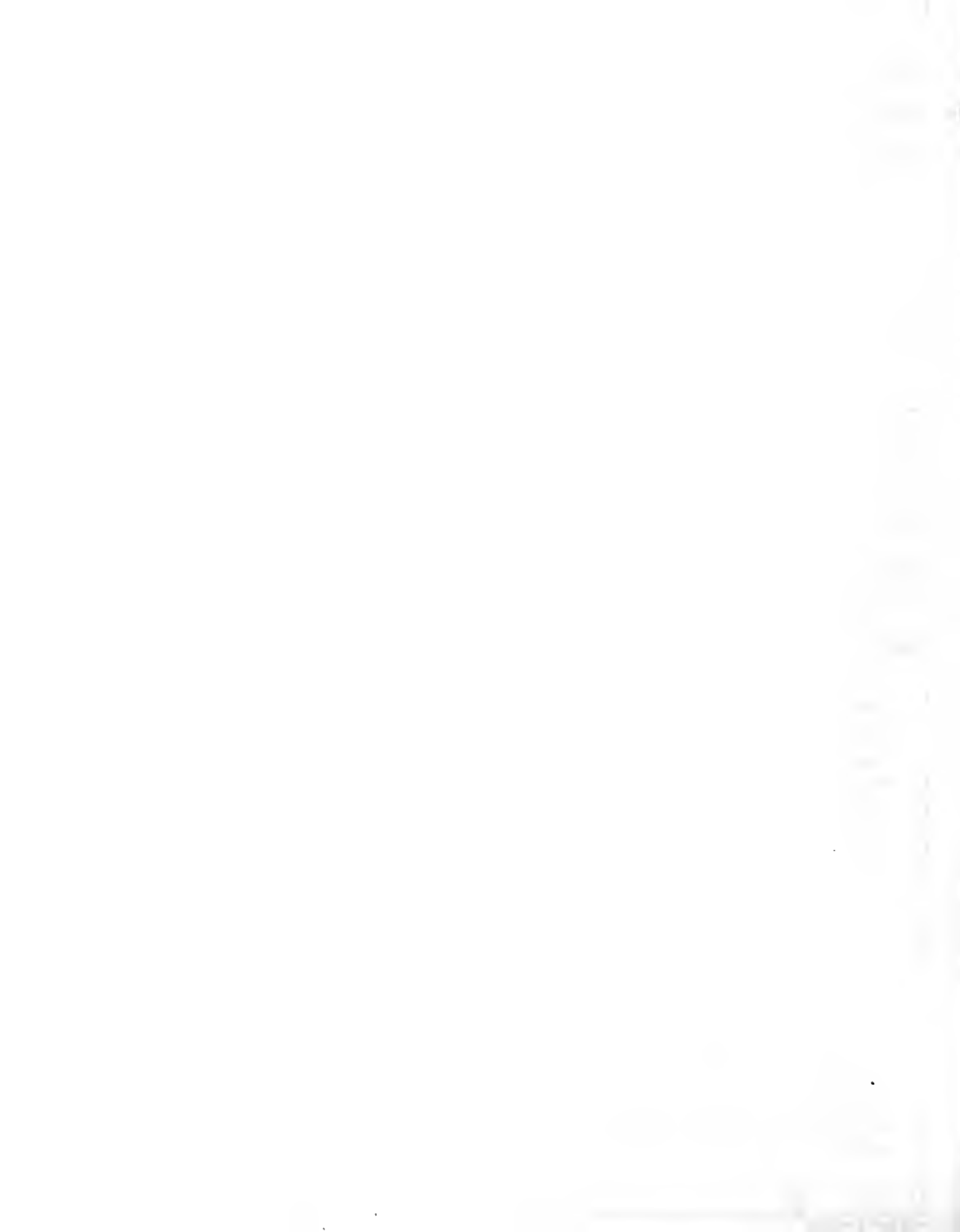
.30

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies of the variability in biological, psychological, and medical phenomena are being carried out to: 1) determine the "normal" range of variability in human aging, 2) identify potential sources of variability which may be responsive to intervention, and 3) determine if there are subgroups of individuals who are susceptible or resistant to various aspects of aging. The research combines the use of sophisticated statistical methodologies and the unique time depth and multidisciplinary breadth of the existing BLSA data base to examine issues related to the concepts of "normal" and "successful" aging, as well as to increase the power of traditional research designs. The statistical methods used include repeated measures analysis of variance, repeated measures regression models, and finite mixture models. Major findings include: 1) within-subject variability in risk factors over time is sufficient to make baseline measurements unreliable estimates of chronic levels of exposure to many risk factors, 2) individuals differ significantly in the rates of change in blood pressure, and 3) the distributions of various biomedical risk factors change with age. These findings represent significant contributions to the theoretical and methodological development of biomedical risk factor studies, as well as to an increased understanding of the dynamics of the aging process. Research is underway to develop more refined methods of studying variability in aging in order to develop theoretically and methodologically sound approaches to risk factor analysis which account for changes in an individual's covariates over time and the possibility that individuals differ in susceptibility or resistance to aging processes.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00638-01 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Health Promotion, Modifiable Risk Factors and Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L.J. Brant Mathematical Statistician LSB, NIA

Others: J.L. Fozard Chief LSB, NIA  
E.J. Metter Medical Officer, BLSA LSB, NIA  
J.D. Pearson IRTA Fellow LSB, NIA

## COOPERATING UNITS (if any)

Division of Health Systems, Johns Hopkins School of Hygiene  
and Public Health (A.H. Sorkin)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.48

## PROFESSIONAL:

.28

## OTHER:

.20

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Unnecessary morbidity and mortality is an important problem which leads to increased health care costs and can ultimately result in premature death. It has been estimated that approximately two thirds of mortality is due to potentially preventable causes - 1.2 million deaths (65%) and 8.4 million years of life lost before age 65 (63%). Principal factors associated with unnecessary mortality include tobacco use, high blood pressure, improper nutrition, lack of screening and prevention services, alcohol abuse, and injury. This project uses data from the Baltimore Longitudinal Study of Aging (BLSA) to examine the influence of modifiable risk factors such as these on the occurrence of premature deaths which have occurred during the 32 years of the study. Using the Health Risk Appraisal (HRA) developed by the Carter Center of Emory University, serum total cholesterol levels, blood pressures, relative body weights and tobacco use of BLSA males who died before age 75 and women who died before age 80 are examined to assess their impact on mortality and modifiability in terms of potential years of life gained. The HRA evaluations indicate that the majority of men and women who died prematurely of heart disease and stroke would have reduced their chances of mortality if they had successfully reduced their cholesterol, blood pressure and body weight. Also, 67% of the men and 40% of the women had an added risk due to cigarette smoking. Similar trends were found for those who died of cancer, except reducing blood pressure was found to be the least successful modifiable risk factor. Results show that 45% of the females who died from cancer were recommended to reduce blood pressure; while 46% of the men received similar recommendations.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00623-02 LSB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of Statistical Methodology for the Analysis of Studies of Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L.J. Brant Mathematical Statistician LSB, NIA

Others: C.H. Morrell IPA LSB, NIA  
J.D. Pearson IRTA Fellow LSB, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.00

## PROFESSIONAL:

.70

## OTHER:

.30

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The applied and theoretical development of statistical methodology is progressing in the areas of biological and epidemiological models, mixture models for describing age changes in distributions of biological markers of morbidity and mortality, multiple comparisons, survival analysis, and the design of experiments, each of which is applicable to longitudinal studies and other studies of aging. The research utilizes various types of statistical models - regression models for studying risk factors' association with outcomes observed in prospective studies, and mixed-effects models for longitudinal data which consider both within- and between-subject variation in analyzing the repeated measurements for all individuals in the study population. Other techniques used include Bayesian, maximum likelihood and numerical computing methods. The methodology created provides original contributions to experimental testing associated with longitudinal studies, simultaneous comparison of various specified experimental effects, epidemiological study of disease states, survival or failure analyses of longitudinal observations representing growth, physical and mental disability, and other biological and behavioral changes in humans and animals. A major emphasis of this research project is on the development of methods which yield cogent yet easily understood results when applied to data. Recent developments in the applications of mixture models show that the distribution of the measurements of biological markers change differently over the adult-age span. For some markers, such as systolic blood pressure, the variability in the distributions increases with age, while for others, such as body mass index, the variability in observed measurements declines with age.



LNG-IRP-NIA

LCMB-IRP-NIA

LCP-IRP-NIA

LBC-IRP-NIA

LBS-IRP-NIA





ANNUAL REPORT OF THE LABORATORY OF BIOLOGICAL CHEMISTRY

NATIONAL INSTITUTE ON AGING

Many changes have happened in the Laboratory of Biological Chemistry during the past year. These include the addition of new personnel, transfer of long-term employees to other programs within the NIA, and the development of new research programs. In general, there has been a concerted effort to convert the Laboratory programs to neuro- and cell- biology. What is most notable is the transfer of employees in the Section on Membrane Biology, including Drs. Froehlich, Cheng, Kinsella, and Mr. Heller, to the Laboratory of Cardiovascular Science. Their assignment is to develop a vascular biology initiative with the idea of examining the changes in blood vessels with age that contribute to some 60% of the deaths in this country. In preparation for this initiative, Dr. Froehlich has been on special assignment at the Max-Planck Institute for Biophysics in Germany, and Dr. Kinsella has been working on the Bethesda campus of the NIH with a group working on endothelial cell differentiation. In addition, Dr. Charles Filburn, a staff scientist, has undertaken a sabbatical assignment at Johns Hopkins University to develop his skills in molecular biology.

MOLECULAR NEUROBIOLOGY UNIT

Dr. Gerald Higgins has been recruited from the University of Rochester to develop an initiative in molecular neurobiology. Dr. Higgins is well known for his studies on the biosynthesis of the amyloid precursor protein, and studies on its involvement in Alzheimer's disease. The four major areas of focus for the new unit will be molecular neuropathology, mechanisms of cell death, neurotrophic factors and molecular biomarkers of Alzheimer's disease.

BONE CARTILAGE STUDIES

Also, we have strongly increased our efforts in the area of bone and cartilage. Dr. Liang is developing a quantitative model for measuring the capacity of bone to regenerate. Removal of bone marrow elicits a massive induction of bone formation in the shaft and marrow space of long bones of rodents. This model provides an ideal system for testing growth factors and gene therapy to restore age-associated deficits in bone. In addition, Dr. Walter Horton has joined the Laboratory from Eli Lilly. His principal interests are in the biology of cartilage and in disorders such as arthritis that alter the function of cartilage.



#### AGING - CANCER

Finally, Dr. Antonino Passaniti has been recruited from Johns Hopkins to initiate studies on cancer and aging and on angiogenesis. A detailed description of these projects is given below.

LMG-IRP-NIA

LCMB-IRP-NIA

LCP-IRP-NIA

LBS-IRP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00051-10 LBC

## PERIOD COVERED

**October 1, 1989 to September 30, 1990**

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Regulation of Mineral Metabolism**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C. Tony Liang	Research Chemist	LBC GRC NIA
Others:		
Shunji Imanaka	Visiting Fellow	LBC GRC NIA
Janice Barnes	Biologist	LBC GRC NIA
Antonino Passaniti	Staff Fellow	LBC GRC NIA

## COOPERATING UNITS (if any)

Dr. Hector DeLuca, Prof., Department of Biochemistry,  
University of Wisconsin

## LAB/BRANCH

**Laboratory of Biological Chemistry**

## SECTION

**Regulatory Mechanisms Section**

## INSTITUTE AND LOCATION

**Gerontology Research Center, NIA, NIH, Baltimore, MD 21224**

## TOTAL MAN-YEARS:

**2.00**

## PROFESSIONAL:

**0.50**

## OTHER:

**1.50**

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes studies on the regulation of intestinal calcium uptake by vitamin D. Impaired intestinal calcium absorption is known to occur in elderly population which contributes to the development of osteoporosis and bone fractures. Using rat as a model, we have shown that duodenal calcium uptake decreases in the senescent rat and the serum concentration of  $1,25(\text{OH})_2\text{D}_3$ , the active form of vitamin D, declines concurrently. This year we attempted to correlate the gene expression of the  $1,25(\text{OH})_2\text{D}_3$  receptor and calbindin, a protein involved in facilitating calcium absorption with the number of receptors and the calbindin content in duodenum of adult and aged rats. We demonstrated a positive correlation which suggests that the deficiency in intestinal calcium absorption observed during senescence can be attributed to the alteration of gene expression of proteins regulated by vitamin D.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00053-02 LBC

## PERIOD COVERED

**October 1, 1989 to September 30, 1990**

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Role of Renal Failure in Age-Associated Changes in Wistar Rats**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.R. Filburn

Senior Investigator

LBC GRC NIA

L. Cheng

Senior Investigator

LCS GRC NIA

## COOPERATING UNITS (if any)

Division of Nephrology, Department of Medicine, University of Southern California (S.G. Massry, G.Z. Fada, X.-J. Zhou)

## LAB/BRANCH

Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.4

## PROFESSIONAL:

0.4

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Insulin secretion was studied in male GRC Wistar rats 6 and 24 mo of age in order to evaluate whether renal failure and hyperparathyroidism frequently observed in senescent male rats plays a role in age-associated reduction in insulin secretion. Senescent rats with chronic renal failure and high PTH exhibited markedly reduced levels of initial phase and total glucose-stimulated insulin secretion from isolated pancreatic islets compared to normal 6 mo adult rats. Insulin secretion from islets from senescent rats with normal renal function and PTH levels was similar to that observed in 6 mo adult rats. The significance of the project lies in the demonstration that impaired insulin secretion by pancreatic islets of senescent rats is not related to age per se, but is associated with chronic renal failure and secondary hyperparathyroidism that develop in many but not all old animals. The results indicate that studies examining the effect of aging on organ function should take into consideration the level of renal function and of serum PTH, since both chronic renal failure and excess PTH are known to adversely affect the functional integrity of many organs.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00054-01 LBC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (30 characters or less. Title must fit on one line between the borders.)

## Molecular Neuropathology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.	G A Higgins	Research Biologist	LBC GRC NIA
Others:	J Kusiak	Pharmacologist	LBC GRC NIA
	C Early	Senior Staff Fellow	LBC GRC NIA
	S Kittur	Senior Staff Fellow	LBC GRC NIA
	H Endo	Visiting Fellow	LBC GRC NIA
	D Norton	Technician	LBC GRC NIA
	C Sherman	Technician	LBC GRC NIA
	E Oh	Special Volunteer	LBC GRC NIA

## COOPERATING UNITS (if any)

Fred Gage University of California, Ken Kosik Harvard Medical School, Elliott Mufson Inst. Biogeront. Res., Rachael Neve Univ. California, Irvine, CA

## LABORATORY

Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS

## PROFESSIONAL

## OTHER

1.0

0.5

0.5

## CHECK APPROPRIATE BOXES)

☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A new program has been initiated in the IRP of the NIA to investigate molecular changes associated with brain aging and Alzheimer's disease. The unit has four major areas of focus: molecular neuropathology, mechanisms of cell death, neurotrophic factors, and molecular biomarkers of Alzheimer's disease. Molecular neuropathology includes studies of aberrant proteolysis of the amyloid precursor protein and amyloid deposition in Alzheimer's disease, differential regulation of *tau* gene expression in Alzheimer's disease, and creation of animal models which mimic the neuropathology of the disease. Mechanisms of cell death includes studies of the structure and regulation of excitatory amino acid receptors and the role of calcium metabolism in neuronal cell death. Neurotrophic factors includes the characterization of novel growth factors and their receptors in the central nervous system, the role of decreased trophic support in neuronal atrophy and death, and studies of trophic activity in extracts of Alzheimer's tissue. Molecular biomarkers of Alzheimer's disease is directed towards the identification of early molecular changes in tissue biopsies obtained from patients in the Baltimore Longitudinal Study of Aging (BLSA), and changes in gene expression in familial Alzheimer's disease pedigrees assayed from cell lines maintained by the NIA.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00055-01 LBC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Age on Osteogenic Activity

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C. Tony Liang

Research Chemist

LBC GRC NIA

Janice Barnes

Biologist

LBC GRC NIA

## COOPERATING UNITS (if any)

Dr. Gideon Rodan, Director, Department of Bone Biology and  
Osteoporosis Research, Merck, Sharp and Dohme Research Lab.  
Dr. Mark Bolander, Director, Osteopaetic Res. Unit, NIAMS

## LAB/BRANCH

Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

0.5

## OTHER:

0.5

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Bone marrow aspiration technique was used to induce a rapid change in bone formation and resorption in rat femur. We have established the time course of gene activation for bone phenotype proteins following the operation. This pattern will be compared to the morphological change to gain an insight to osteogenic function. Sufficient femur RNA samples have been prepared from rats of different ages that should allow us to study the effect of age on osteogenic activity.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00056-01 LBC

## PERIOD COVERED

**October 1, 1989 to September 30, 1990**

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Characterization of Mitochondria-Associated Tumor Hexokinase**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

C.R. Filburn

Senior Investigator

LBC,NIA

## COOPERATING UNITS (if any)

Laboratory of Molecular Bioenergetics, Department of  
Biological Chemistry, Johns Hopkins University School of  
Medicine (P.L. Pedersen, K.A. Arora)

## LAB/BRANCH

Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS

0.8

## PROFESSIONAL

0.8

## OTHER

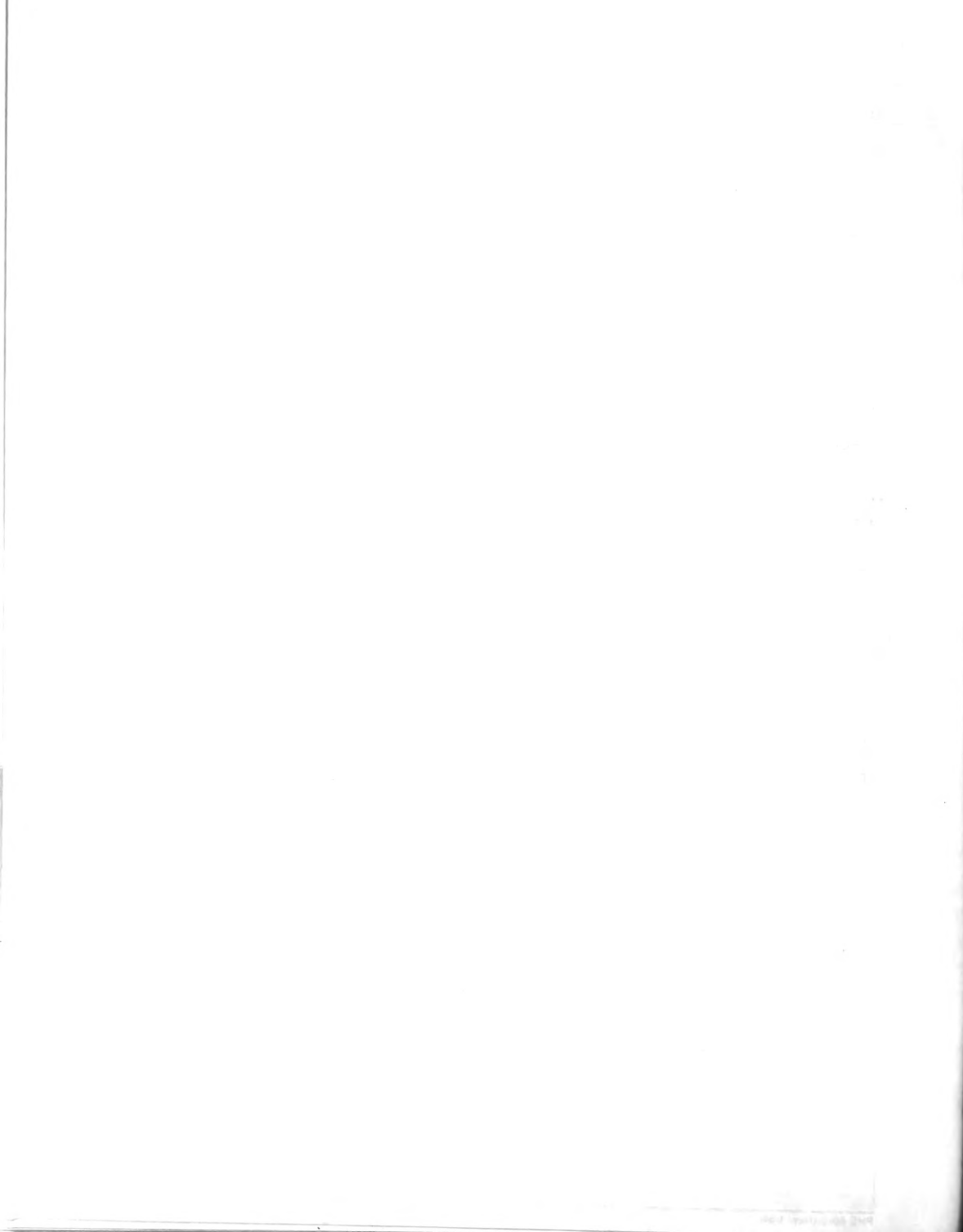
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## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The importance of amino acid residues considered, on the basis of X-ray diffraction studies and conservation of position in glucose-phosphorylating enzymes from yeast to mammalian brain, to be essential for catalytic activity of hexokinases was investigated. A serine residue at position 603 in tumor hexokinase was found to be essential for activity, since more than 90% of wild type activity was lost upon changing it to alanine. A derivative of this ongoing study was the discovery that overexpression of hexokinase or any other protein inserted into a plasmid containing the phosphate-regulated pho A promoter causes induction of a glucose-phosphorylating enzyme distinct from the hexokinase being studied.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00057-01 LBC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Regulation of Matrix Gene Expression in Aging and Disease**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Walter E. Horton, Jr. Guest Researcher LBC GRC NIA

## Others:

C. Tony Liang Research Chemist LBC GRC NIA

Richard Balakir Chemist LBC GRC NIA

Patricia Precht Biologist LBC GRC NIA

Julie Middleton Student Aide LBC GRC NIA

Lynn Shin Summer Program LBC GRC NIA

Mary Sestille Special Volunteer LBC GRC NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

Gerontology Research Center, NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

0.5

## OTHER:

0.5

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Bone and cartilage are sensitive to alterations that result in age-associated diseases such as osteoporosis and osteoarthritis. We are studying the regulation of matrix genes expressed by chondrocytes and related cells. Type II collagen is important for cartilage function and we have identified DNA sequences that are responsible for the chondrocyte-specific expression of this gene. Initial studies indicate that chondrocytes contain unique patterns of DNA binding proteins that are different from those obtained from prechondrogenic mesenchyme cells. Next, we will identify the target DNA sequence for these chondrocyte-specific proteins as the first step in the isolation, characterization, and cloning of these proteins. In addition, we are studying the regulation of the cartilage proteoglycan gene by vitamin D. This may serve as model system for analyzing the molecular action of this important hormone involved in bone formation. A third project involves the regulation of collagen and collagenase gene expression in synovial cells isolated from osteoarthritis (OA) or rheumatoid arthritis (RA) patients and the response of these cells to cytokines. Interleukin-1 induces collagenase mRNA in both cell types with the induction occurring to a greater extent in RA versus OA synovial fibroblasts. Other projects are ongoing assessing the histopathology of articular cartilage in aging Wistar rats and examining the induction of stem cell proliferation and differentiation in bone.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00058-01 LBC

## PERIOD COVERED

**October 1, 1989 to September 30, 1990**

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Tumor growth and metastasis in the aged**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

**Antonino Passaniti Senior Staff Fellow LBC GRC NIA****Others:****Joseph Haney SIS, Part-time LBC GRC NIA****Timothy Cujdik Summer Fellow LBC GRC NIA****Walter Horton Guest Researcher LBC GRC NIA****Linda Cheng Research Chemist LBC GRC NIA**

## COOPERATING UNITS (if any)

**J. Isaacs JHU, B. Carter FSKMC,  
J. LaTerra Kennedy Institute, M. Plunkett Schering-Plough,  
H. Kleinman NIDR, R. Fridman Molecular Oncology**

## LAB/BRANCH

**Laboratory of Biological Chemistry**

## SECTION

**Regulatory Mechanisms Section**

## INSTITUTE AND LOCATION

**Gerontology Research Center, NIA, NIH, Baltimore, MD 21224**

## TOTAL MAN-YEARS:

**1.0**

## PROFESSIONAL:

**0.5**

## OTHER:

**0.5**

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

A program to study the relationship between aging and cancer was initiated in the laboratory. Three human prostatic carcinoma cell lines did not grow when injected in nude mice at levels of 500,000 cells/mouse. However, we obtained very rapid growth of the cells when injected as a suspension with basement membrane. Attempts to address the mechanisms(s) of growth stimulation are on-going and include the effect of laminin peptides and anti-macrophage serum on growth. We are also using isolated primary prostate biopsy tissue to determine if cells from this source will also be stimulated to grow in the presence of extracellular matrix. The growth of tumors in aged mice was studied using C57-BL/6 mice and melanoma cells. These cells were grown subcutaneously and growth was enhanced when cells were injected with extracellular matrix molecules, but enhancement was 3.5-fold more pronounced in 6 mo. old animals compared to 12, 18, and 24 mo. old animals. Further experiments will examine the dose dependence of growth in the aged animals in order to understand the basis for these age-related effects. To examine the initial steps in the metastatic process, microvasculature endothelial cells were isolated from bovine retina and cultured with growth supplements. Activated endothelia was then used to examine tumor cell binding in an *in vitro* assay. These studies will be extended to test inhibitors of glycosylation for their effect on tumor cell adhesion.



LMG-IRP-NIA

LCMB-IRP-NIA

LCP-IRP-NIA

LBS-IRP.



## ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

### NATIONAL INSTITUTE ON AGING

The Laboratory of Behavioral Sciences (LBS) comprises of two sections: Behavioral Physiology (BPS) and Behavioral Medicine (BMS). Since there is considerable interchange between these sections and most of the projects in one section are integrated with projects in the other section, this summary will review the research from various projects, and will merely identify the section most closely associated with that aspect of the program.

#### Nocturnal Hemodynamics

There is an extensive program of research in LBS examining nocturnal hemodynamic patterns and some of their clinical implications. Studies in monkeys have described a nocturnal hemodynamic pattern characterized by a monotonic fall in heart rate, cardiac output, and central venous pressure, and a monotonic rise in total peripheral resistance. Blood pressure falls early in the evening but does not change throughout the night, and stroke volume also does not change overnight. We have interpreted this finding to indicate that there is a normal, nocturnal fall in plasma volume in all primates--it is known that plasma volume falls overnight in man. In order to determine whether the fall in cardiac output was the result of a fall in heart rate, or whether the fall in heart rate was merely a preferred mechanism for accommodating a fall in plasma volume, we implanted atrial demand pacemakers in a group of animals and compared their hemodynamic responses under control conditions to their responses during pacing when heart rate was not allowed to fall overnight. The main finding was that when heart rate was not allowed to fall at night, stroke volume fell indicating that the fall in cardiac output was a necessary occurrence. We also observed a complex sequence of events over the 20-day interval of pacing compared with the control condition: preventing heart rate from falling was associated with a significant rise in left ventricular work and a decline in cardiac performance characteristic of heart failure. These data suggest that one of the functions of sleep may be to allow the heart muscle to rest. All of the findings noted above were carried out in BPS; however, they have generated clinical hypotheses that are now being tested in studies in BMS.

One study is designed to test the hypothesis that the nocturnal fall in plasma volume may contribute to the morning increase in occurrence of episodes of silent ischemia; and the second study is designed to test the effect of pacemaker rate on cardiac function in patients with implanted atrial demand pacemakers. These studies have just begun; however, they illustrate how the programs in LBS interrelate. It was noted above that the nocturnal hemodynamic patterns described above are characteristic of primates. That is because one study recently finished in BPS has shown that this pattern does not occur in the dog. We believe this species difference occurs because of fundamental behavioral



differences between primates and dogs: primates sleep throughout the night whereas dogs awaken frequently to drink or to eat. Thus, whereas plasma volume falls in primates because they lose fluid overnight without replacement, dogs continuously replenish their fluid volumes.

Given the close relationship between cardiovascular function and pulmonary function, it is not surprising that many of the projects in BMS are directed at that relationship. One such project is the study of respiratory factors in blood pressure regulation. In the dog study cited above, in addition to the blood pressure effects already noted, there were also significant alterations in cardiopulmonary function during the waiting period. Specifically, the animals evinced a bradycardia, an increase of total peripheral resistance, and a reduction in ventilation. Investigators in BMS have developed an ambulatory monitor which permits them to measure tidal volume and breathing frequency in people as they go about their daily activities. This device will enable investigators to test the interaction between naturally-occurring daily events, and cardiopulmonary function. Baseline studies with this system already have shown that frequently during the day there are falls in breathing frequency below sleep levels that are not compensated by increases in tidal volume. Furthermore, these episodes are more likely to occur in the presence of other people but are not mediated either by talking, per se, or by physical activity. Future studies in this program will include detailed behavioral diaries which may help to characterize the environmental conditions that are more likely to mediate significant





cardiopulmonary effects. Studies in BPS in the micropig laboratory also should help to characterize some of the behavioral mechanisms involved.

Additional studies in BMS are examining the role of diaphragmatic breathing in the cardiopulmonary function of patients with sleep apnea. These studies have shown that when these patients are compared to matched control subjects, they have an greater abdominal component of breathing at rest which is not secondary to their obesity. In addition, they respond with greater increases in systolic blood pressure during performance of an abdominal breathing task.

### Thermoregulation

Clinical experience has shown that elderly persons do not cope well with thermal stress: either extreme cold or extreme heat. Laboratory studies with rodents also have shown clearly that one of the first indices of physiological, age-related decline, is a fall in body temperature. Since thermoregulation is commonly mediated by behavioral, as well as metabolic mechanisms, several projects in BPS have been directed at this problem. Several studies have shown that aged mice are less able to maintain body temperature in response to repeated cold exposures than are adult animals. Studies completed this year have shown clearly that old animals evince a reduced capacity for metabolic heat production as well as a reduced capacity for heat conservation. The decline in heat production is probably primarily related to changes in metabolic activity in brown adipose tissue (BAT). Ongoing studies show that thermogenin mRNA induction during cold stimulation is similar in old and adult mice indicating that aged animals have not lost the ability to sense cold or to synthesize thermogenin mRNA. Nevertheless, GDP binding studies indicate a reduction in thermogenin synthesis in old animals suggesting that there is a defect either in their ability to synthesize protein or in post-translational processing. Studies of heat shock protein suggest that this moiety is induced by a variety of stimuli and is not specifically related to thermogenesis. BALB/cHeA mice are interesting subjects for studies of thermoregulation since these animals are deficient in glycerol-3-phosphate dehydrogenase, an enzyme which is probably important in BAT thermogenesis through its role in triglyceride synthesis and the glycerol phosphate shuttle. Collaborative studies with investigators at Jackson Laboratories have shown that male (but not female) BALB/cHeA animals had better cold tolerance than did a control strain (BALB/cByJ). Nevertheless, metabolic heat production between these animals was not different. These findings suggest that the deficiency in nonshivering thermogenesis in these animals could be overcome by increased shivering thermogenesis as well as by superior heat conservation. Nor-adrenalin has been clearly established as a natural stimulus to heat production in BAT. However, it is not clear whether this effect is mediated through direct, sympathetic nervous innervation of BAT parenchymal tissue, or whether the nor-adrenalin comes from other organs such as the adrenal medulla and vascular nerve endings. Collaborative studies between BPS investigators and scientists at Tokyo Metropolitan Institute of Gerontology (TMIG) have traced nerves entering interscapular, BAT tissue in cold-unadapted mice and found that most of these nerves either pass through to skin or muscle, or terminate in blood vessels. During cold exposure nerve



activity to skin or muscle increases suggesting sympathetically-mediated vasoconstriction, whereas nerve activity to BAT decreases suggesting vasodilatation. Following unilateral denervation, interscapular blood flow to the innervated side increases as rectal temperature falls; however, on the denervated side there is very little change in temperature. All of these findings suggest that BAT parenchymal tissue does not receive direct sympathetic innervation in the cold-unadapted animal. The collaboration with TMIG will continue; studies of cold-adapted and adult and old mice will be implemented since these findings suggest that age-related changes in vascular response may be important factors in the decline in cold-tolerance of older animals.

### Urinary Incontinence

Urinary incontinence is a major clinical problem for the elderly. It has been estimated that about \$10 billion in direct costs are invested annually in this problem. There is no estimate of the indirect costs, e.g., the role of incontinence in the decision of a family to admit an elderly relative to a nursing home. Investigators in BMS have developed powerful, behavioral treatments for the most common kinds of incontinence occurring in community-dwelling elderly; and these methods are now widely used in clinical practice in several countries throughout the world. In the nursing home, at least 50% of the residents are incontinent. Studies in LBS have shown that for many of these residents, the incontinence is attributable to an inability of the resident to toilet himself or herself. Recently, LBS completed a major research project which showed how a staff management program could be designed and implemented to increase resident toileting. Several studies by LBS investigators have shown that incontinence is not consistently documented in the medical record, and that care plans are not consistently developed for managing incontinence. Studies are now underway to determine if the staff management program we developed can be effective in improving clinical practice.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00063-22 LBS

PERIOD COVERED  
October 1, 1989 to September 30, 1990TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Learned Modification of Visceral Functions in Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Bernard T. Engel, Chief, Laboratory of Behavioral Sciences LBS, NIA

OTHERS: Mark I. Talan, Medical Officer (Research) LBS, NIA

## COOPERATING UNITS (if any)

Department Comparative Physiology, Eotvos Lorand Univ., Hungary (G. Adam, G. Bardos),  
Johns Hopkins Univ., Division of Cardiology, Francis Scott Key Medical Center (P. Chew)

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

1.5

## OTHER:

2.5

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments we are studying the extent to which the cardiovascular system can be modified by instrumental conditioning. In other experiments, we are examining diurnal patterns of hemodynamic performance.

We have developed and tested a system for continuous recording of cardiovascular parameters in unrestrained tethered monkeys.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00072-05 LBS

PERIOD COVERED  
October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral Assessment and Treatment of Incontinence in Nursing Home Residents

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Bernard T. Engel, Chief, Laboratory of Behavioral Sciences LBS, NIA

OTHERS: Kathleen A. McCormick, Nursing Research Director LBS, NIA

## COOPERATING UNITS (if any)

Univ. Pittsburgh School of Medicine, Pittsburgh, PA (L. Burgio and K. Burgio); Francis Scott Key Medical Center (A.S. Scheve); Health Care Financing Administration

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.40

## PROFESSIONAL:

.30

## OTHER:

.10

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Incontinence is a major reason for institutionalizing elderly persons and is common in nursing homes. This project is designed to evaluate the effectiveness of behavioral treatment techniques as well as staff management techniques.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00073-0 2 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physiology of Thermoregulation and Aging in Rodents

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Mark I. Talan, Medical Officer (Research)

LBS, NIA

OTHERS: Bernard T. Engel  
Hal TatelmanChief  
Staff FellowLBS, NIA  
LBS, NIA

## COOPERATING UNITS (if any)

Laboratory of Molecular Genetics, NIA (N. Holbrook, M. Blake); Jackson Laboratories, Bar Harbor, MA (L. Kozak); Tokyo Metropolitan Institute of Gerontology (A. Sato, Y. Sato)

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center Baltimore, MD 21224

TOTAL MAN-YEARS: 4.1

PROFESSIONAL: 2.4

OTHER: 1.7

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The purpose of this project is to investigate age-related changes in thermoregulation and to examine the physiological mechanisms underlying these changes.

We have demonstrated that aged mice have diminishing cold tolerance and are not able to adapt to repeated cold exposure. The cause of these age-related aberrations in thermoregulation appears to be, in part, a reduction in metabolic heat production and, in part, a reduction in heat conservation mechanisms. During the life span, the relative contributions of heat production and heat conservation mechanisms to cold tolerance change.

The results from a number of experiments suggest that the mechanism responsible for diminished metabolic heat production in response to cold is an age-related change in brown adipose tissue. Collaborative studies with scientists at the Tokyo Metropolitan Institute of Gerontology suggest that these changes are associated with changes in vascular function.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 000600-02 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Respiratory Factors in Blood Pressure Regulation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David E. Anderson, Chief, Behavioral Medicine Section

LBS, NIA

OTHERS: Jennifer A. Haythornthwaite, IRTA Fellow

LBS, NIA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.8

## PROFESSIONAL:

.4

## OTHER:

.4

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Previous studies have established that sustained hypertension develops over periods of days and weeks in laboratory animals exposed to a combination of high sodium intake and a behavioral conditioning procedure which induces respiratory suppression, bradycardia, and peripheral vasoconstriction. The present project extends this paradigm to an analysis of the environmental factors involved in long-term blood pressure control of human subjects and patients with hypertension. The project is based on the hypothesis that episodes of respiratory suppression in the natural environment are an index of a physiological stress response which increases cardiovascular sensitivity to sodium intake. A respiration monitor has been developed which enables continuous noninvasive monitoring of ventilatory frequency and tidal volume of ambulatory human subjects. Initial studies with the monitor showed that episodes of respiratory frequency suppression to levels significantly below those in sleep do occur, without compensation in tidal volume. Subsequently, it has been found that these episodes occur disproportionately in the presence of other people, and that they are not due to talking, per se, or to physical activity. Thus, specific social stresses may influence endocrine responses involved in sodium regulation. Further studies are addressing the nature of the social settings which may evoke this response and its cardiovascular consequences.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 000601-02 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Exercise Influences in Aging Man

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Kathleen A. McCormick Nurse Research Director LBS, NIA

OTHERS: David E. Anderson Chief, Behavioral Medicine Section LBS, NIA  
Bernard T. Engel Chief, Laboratory of Behavioral Sciences LBS, NIA  
Ricardo A. Brown IRTA Fellow LBS, NIA  
Reubin Andres Chief, Laboratory of Clinical Physiology LCP, NIA

## COOPERATING UNITS (if any)

Baltimore Longitudinal Studies Branch, NIA (J. Metter); Pulmonary Epidemiology Division, Johns Hopkins Univ. and BLSA Pulmonary Consultant (M. Tockman); NY City Opera; Wolf Trap Farm Park, VA

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

1.0

## OTHER:

.5

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

This project is concerned with experimental differentiation of cardiopulmonary deficits associated with aging versus pathophysiology. One set of projects involves the application of an abdominal breathing task to the study of and intervention in selected pulmonary disorders. A study during the past year focused on the abilities of opera singers, wind instrumentalists, and other opera company members, to self-control abdominal breathing as evidence for the effects of training in retarding deterioration of pulmonary function with age. Another project assesses the utility of Doppler technology in studies of the effects of aging on cardiac functions. Work over the past year has shown that the Doppler index of cardiac stroke volume varies inversely with heart rate changes as subjects assume recumbent sitting and standing postures, respectively. Together, these studies define age-related cardiopulmonary function changes associated with training influences versus disease.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 000602-02 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Diaphragmatic Breathing Challenge in Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Kathleen A. McCormick, Nursing Research Director

LBS, NIA

OTHERS: David E. Anderson

Chief, Behavioral Medicine Section

LBS, NIA

Bernard T. Engel

Chief, LBS

LBS, NIA

Ricardo A. Brown

IRTA Fellow

LBS, NIA

## COOPERATING UNITS (if any)

Sleep Lab, Francis Scott Key Medical Center and The Johns Hopkins University School of Medicine (Phil Smith); Baltimore Longitudinal Studies Branch, NIA (James Fozard)

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS: 2.2

PROFESSIONAL: 1.2

OTHER: 1.0

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is concerned with the integration of behavioral principles with physiological measurement for application to clinical medicine. Subjects are normal volunteers recruited from the BLSA and/or the community who are studied to provide normative data on the response of persons with normal hearts and lungs to a breathing challenge using their diaphragm. Comparative groups are patients selected from various medical clinics who are characterized and compared with the normal volunteers. If the performance of those persons with pathophysiology is determined to be less than normal, or volunteers or groups of persons who are high-performers, behavioral techniques can be applied in training subjects to breathe diaphragmatically and improve cardiopulmonary response. If the breathing challenge is an exercise, then the comparison of this test to standard, graded exercise tests could improve the description of cardiopulmonary performance in normal, aged persons and those with pathophysiology.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00603-01 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Implications of Nocturnal Hemodynamic Events

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Bernard T. Engel, Chief, Laboratory of Behavioral Sciences LBS, NIA

OTHERS: Mark I. Talan, Medical Officer (Research) LBS, NIA

## COOPERATING UNITS (if any)

Johns Hopkins University School of Medicine, Division of Cardiology (Paul Chew);  
Francis Scott Key Medical Center, Baltimore, MD

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.30

## PROFESSIONAL:

.20

## OTHER:

.10

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies in animals have shown significant nocturnal hemodynamic patterns which may contribute to morbid changes in cardiovascular function in patients with heart diseases. This project is designed to evaluate diurnal cardiovascular effects in select patient groups.



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 AG 000604-01 LBS

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral Factors in Blood Pressure Regulation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David E. Anderson, Chief, Behavioral Medicine Section

LBS, NIA

OTHERS: Jennifer A. Haythornthwaite IRTA Fellow

LBS, NIA

Richard E. Pratley

Medical Staff Fellow

LCP, NIA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Behavioral Sciences

SECTION

Behavioral Medicine Section

INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.0

PROFESSIONAL:

1.0

OTHER:

1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects

☐ (b) Human tissues

☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The role of dietary sodium chloride in the pathogenesis of primary hypertension has remained enigmatic. Insight into its possible contribution may be provided in animal studies which have shown that high sodium intake engenders sustained hypertension if, and only if, the subject is concurrently exposed to recurrent behavioral stress. Accordingly, the present project addresses the hypothesis that a high sodium intake will elevate blood pressure in humans, but only under specific life stress conditions associated with neuroendocrine-mediated effects on sodium regulation. An initial study is being conducted with medical students maintained on a high sodium diet or placebo for two weeks immediately preceding their final exams. Preliminary results show that resting blood pressure increased during the two weeks prior to examinations in subjects on a high sodium diet but not on the placebo. In addition, subjects in the high sodium group reported changes in perceived stress and state anxiety which were significantly correlated with the magnitude of pressure elevation. These results are consistent with the hypothesis that interactions of stress and salt intake have significant effects on long-term blood pressure regulation, and provide a basis for further investigation of mediating physiological and cellular factors.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 000605-01 LBS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cardiovascular Interactions of Stress and Salt in the Micropig

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David E. Anderson, Chief, Behavioral Medicine Section

LBS, NIA

OTHERS: Michael Crowell, Guest Researcher

LBS, NIA

## COOPERATING UNITS (if any)

None

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine Section

## INSTITUTE AND LOCATION

NIA, NIH, Gerontology Research Center, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.4

## OTHER:

.6

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The micropig is an excellent animal model for study of long-term blood pressure regulation because of (a) the similarity of its cardiovascular system to man, and (b) the fact that interactions with humans during experimentation pose fewer logistical problems than either primates, who may be aggressive, or dogs, who are naturally affiliative. A technology for study of long-term cardiovascular functions in the chronically instrumented and behaving micropig has been developed for study of interactions of stress and salt intake. The specific hypothesis under investigation is that behavioral stress which evokes respiratory suppression, bradycardia, and peripheral vasoconstriction also increases circulating concentrations of an endocrine factor which suppresses sodium pump activity. Confirmation of this hypothesis would provide a significant advance concerning the role of environmental and behavioral factors in long-term blood pressure regulation. Increased ability for nonpharmacological self-regulation of blood pressure could impact on a number of cardiovascular disorders of aging, including stroke.



LCB-IRP-NIA

LCB-IRP-NIA

LCB-IRP-NIA

LCB-IRP-NIA





## Laboratory of Cellular and Molecular Biology

This laboratory conducts fundamental research on some of the basic systems of molecular biology as well as studies designed to understand the biology of aging. The laboratory was not designed to operate in a pyramidal mode, in which the laboratory chief formulates a grand design. Rather it was organized to bring together sections led by investigators with a diversity of goals but also a community of interests.

The Inorganic Biochemistry Section has conducted many studies on nucleic acid structure and function as well as a variety of studies on molecular structural changes in aging. A particular emphasis at the moment is the project on the mechanism of RNA synthesis at the site of internucleotide bond formation, leading to a model of structure in the active site of RNA polymerase that is compatible with the functions of the enzyme. The section has just completed a monumental effort to compile all the data on the interaction of metal ions with DNA and RNA. The section has begun a systematic study of the metabolic effects of exercise as part of the Baltimore Longitudinal Study on Aging.

The Molecular Dynamics Section shares the commitment to structural studies with the Inorganic Biochemistry Section, and is actively collaborating on the RNA synthesis study. Its importance is signified by its title - the emphasis on the dynamics, i.e. molecular motion that occurs during - and is required for - biological function. The section is presently involved in characterizing the dynamics of the interaction of hemoglobin with oxygen and other ligands, having identified distal perturbations and subunit interactions across the  $\alpha_1\beta_1$  interface as important components in the process. It is also engaged in studying the consequences of the discovery of enhanced hemoglobin oxidation rate under hypoxic stress resulting in the formation of superoxide.

The Macromolecular Chemistry Section has carried out a variety of activities designed to understand the molecular basis of drug action and to lead to the design of better drugs. The work has been centered on the reaction of  $\alpha$  and  $\beta$  blockers with their receptors and on the synthesis of macromolecular drugs based on cyclodextrin. Recent work has been focused on the cyclodextrin studies, and has led to the development of techniques for binding adducts to specific sites on the cyclodextrin molecule.

The Molecular Physiology and Genetics Section is dedicated to the study of the regulation of physiological functions during aging. The studies on age changes in hormone and transmitter action involve adrenergic receptors and are therefore related to the work of the macromolecular chemistry section. The section is also studying age changes in central nervous system responsiveness, behavioral biology, gene expression and the biology of human longevity. It is also involved in determining whether caloric modification increases lifespan in primates as well as in previously studied rodents.

Following are some of the highlights of the research in each section:



## Inorganic Biochemistry Section

### Mechanism of RNA Synthesis

Previous studies on the geometrical relationship between the two substrates and the two enzyme-bound metals at the active site of E. coli RNA polymerase had shown flexibility at this active site, as indicated, by changes in the distance between the metals in the i and i+1 sites. We postulated that this flexibility could be useful in enabling the enzyme to differentiate between "correct" and "incorrect" incorporation of ATP's and thus to insure the accuracy of transcription. To test this hypothesis we are studying the geometric relationships with complementary and non-complementary template - substrate combinations. The hypothesis predicts that the complimentary combinations, which could introduce the "correct" substrates would lead to a different conformation from that produced by a non-complementary combination, which would introduce "incorrect" substrates.

We are close to completion of such a comparison, in which non-complementarity is produced with poly(dAdT).poly(dAdT) template and two ATP substrates, and complementarity with poly(dT) template and 3'dATP substrates. In the former case actual RNA synthesis was prevented (to make the NMR studies possible) by the non-complementarity. In the latter case it was prevented by the elimination of the 3'OH group from the substrates. Before the template-substrate interaction effects can be ascertained, it was necessary to determine whether the placement of 3'dATP instead of ATP into the substrate sites would alter the interaction geometry. Apparently that does not occur since the metal - metal distances are the same in both cases.

Addition of template, however, has opposite effects on the complementary and non-complementary systems (decrease and increase in metal - metal distance, respectively). This comparison provides evidence for the hypothesis that the enzyme assumes two different conformations for "correct" and "incorrect" substrates. Proof of the hypothesis can be obtained from a second comparison between another set of complementary and non-complementary reactants.

### Active and Inactive Forms of RNA Polymerase

Extensively purified preparations of E. coli RNA polymerase (RNAP) have commonly been found to exhibit lower transcriptional activity than expected if each protein molecule were fully active in every phase of transcription. Fractional activities from 30 to 80% generally have been reported, based on the generation of transcripts on a defined template. The shortfall in measured activity could be due to damaged RNAP molecules; on the other hand, it could result from an equilibrium between active and inactive (or less active) states of the enzyme, that plays a role in one or more of the stages of transcription. We obtained independent evidence for RNAP molecules that are inactive during transcription by extracting the transcription reaction with the polyanion heparin. Two RNAP fractions appeared that did not take part in elongation. In this and other analysis of RNAP activity we have used T7 phage DNA, which has one strong promoter recognized by the E. coli enzyme.



To further explore the apparently inactive fractions, we trapped all the template-bound RNAP through DNA absorption to a cationic matrix, DEAE-Sephrose, at relative low salt, then released at high salt the RNAP not engaged in the strongly DNA-bound elongation complex. Very little RNAP was not trapped at low salt. A reasonable proportion of the RNAP was released by high salt (compared with the shortfall in activity), and it displayed activity in a subsequent transcription cycle. Additionally, we have found that the activity measured for an RNAP sample can depend on the concentration at which the RNAP is introduced into the transcription reaction and allowed to bind to the DNA. Dilution led to lowered apparent activity; and re-concentrating such diluted RNAP restored the measured activity toward the value obtained by direct addition of the undiluted RNAP to template. These findings suggest that a conformational equilibrium may exist between active and "inactive" forms of the enzyme. These studies have not differentiated between inactivity that may be a desired attribute of the enzyme somewhere in the transcription process, and an inactivity due to preparative damage. If it is the latter, however, our studies show that the damage can apparently be reversed. Thus activity measurements by the accepted techniques do not appear to be reliable indexes of functionality.

### Molecular Dynamics Section

#### Subunit Interactions in Hemoglobin

Our earlier studies with valence hybrids relate to the importance of  $\alpha_1\beta_1$  interactions within the high affinity R quaternary state. These interactions have been associated with the enhanced autoxidation of triliganded hemoglobin. We have now in collaboration with Vijay Sharma of the University of California at San Diego, shown that the  $\alpha_1\beta_1$  interface also plays a role in the binding of the first two ligands to tetrameric T-state hemoglobin. Thus interactions across the  $\alpha_1\beta_1$  interface also modulate the functional ligand binding properties of hemoglobin.

#### Oxidation of Hemoglobin

We have proposed that distal perturbations associated with the removal of the first oxygen are responsible for the enhanced autoxidation.

In order to understand this phenomenon molecular dynamics simulations have been performed. The ability of the distal histidine to H-bond with ligands in the pocket has been well documented. We have, however, demonstrated that it is energetically feasible for the distal histidine to approach the iron forming a bond and to even displace a bound ligand. These interactions were shown to be dependent on the detailed configuration of the distal pocket with clear differences noted between  $\alpha$ -chains and  $\beta$ -chains. Nucleophilic displacement of the bound oxygen with the release of superoxide is considered necessary for autoxidation. Most studies postulate the role of exogenous nucleophiles. On the basis of our simulations the involvement of the endogenous distal histidine as a nucleophile can be postulated. As seen by the comparison between  $\alpha$ -chains and  $\beta$ -chains, this reaction is very sensitive to changes within the ligand pocket and even small perturbation can thus produce a large enhancement of the rate of autoxidation.



### The Hypoxic Stress on Erythrocytes

Autoxidation of hemoglobin with the production of superoxide at the reduced oxygen pressures corresponding to partially oxygenated hemoglobin has been found to produce enhanced lysis. However, the maximal amount of superoxide which escapes the endogenous superoxide was found at much lower pressures, for which the hemoglobin is nearly completely deoxygenated.

It was possible to show, by experiments with erythrocyte ghosts, that the release of superoxide at low oxygen pressure requires the presence of membranes and reduced Fe(II) hemoglobin. Recent studies indicate that deoxyhemoglobin has a higher affinity for the cytoplasmic end of the integral membrane protein band 3, which also contains the anion channel. We have been able to implicate binding of hemoglobin to band 3 at low oxygen pressure with the release of superoxide. Thus superoxide formation is eliminated when band 3 reacts with diisothicyanostilbene 2,2' disulfonic acid (DIDS).

### The Erythrocyte Hypoxic Stress and Aging

In order to evaluate the effect of age on the hypoxic stress associated with the formation and release of superoxide, studies have been performed both as a function of cellular age and subject age. Results on humans indicate that cellular aging of mature erythrocytes enhances the formation of superoxide, which escapes the endogenous superoxide dismutase, as well as the lysis. However, no changes were resolved for individual aging even though a younger distribution of cellular ages are found for older subjects. Additional experiments with rats in collaboration with David Danon confirm that older animals possess a younger distribution of cells without producing the expected decrease in the hypoxic stress. Studies with animals bled to increase the number of young erythrocytes suggest that this dichotomy can be explained by enhanced leakage of superoxide for the very young cells when they are first put into circulation, particularly in older subjects. This phenomenon cancels out any advantage to older subjects due to a younger cell distribution and suggests possible difficulties in the hemopoietic system which exacerbate hypoxic stress in older subjects.

## Macromolecular Chemistry Section

### Chemistry of Cyclodextrins

From the results of analysis of the samples prepared in the Macromolecular Chemistry Section substitution rules for the reaction of cyclodextrin with propylene oxide were deduced. On the basis of these rules individual 2-O and 6-O 2-hydroxypropylcyclodextrins were synthesized. These 2-O and 6-O derivatives were found to differ dramatically in their ability to form crystalline complexes with lipophiles. Simultaneously, with our studies, Dr. Harata evaluated crystal structures of our compound and eventually his results explained the observed difference in complexation ability. The 2-O derivatives in the crystal are self-associated in a manner that the substituent of one cyclodextrin is inserted into the cavity of another cyclodextrin; consequently

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there is cavity space to accommodate a guest lipophile. The 2-0 derivatives are thus both the host and guest components of the host-guest complexes.

### Steroid Hormones and Cyclodextrins

Complexes were prepared of a series of steroids with hydroxypropylcyclodextrins and these were subsequently used by our collaborator, Dr. G. Taylor, to examine the androgen-sensitive behavior and physiology in gonadally intact male rats. The animals studied received daily injections of steroids (0.4 mg/kg) in two pharmaceutical forms for one month. When steroids were injected as aqueous solutions of hydroxypropyl- $\beta$ -cyclodextrin complexes, a form which insures a rapid distribution through the organism, testosterone strongly increased behavior parameters, while its precursors (dehydroepiandrosterone and 4-androstene-3, 17-dione) and its metabolite (5- $\alpha$ -dihydrotestosterone) decreased them. This suggests that supplemental pulses of precursors do not propagate through metabolic conversions to lead to an effective testosterone pulse. The treatments did not affect sperm counts in epididymis. The size of ventral prostate was increased only after the administration of 4-androstene-3, 17-dione or 5- $\alpha$ -dihydrotestosterone, but not after testosterone or dehydroepiandrosterone. When steroids were injected in oil, a pharmaceutical form which distributes steroids slowly and in a protracted manner, testosterone led to an increase in behavior parameters, and to enlargement of the prostate. The suppression in behavior and prostate enlargement by other steroids were more pronounced than when these were administered in complexed forms. Obviously, some of the adverse effects of the presently used depot steroid preparations are of pharmacokinetic origin.

### Cyclodextrin Sulfates and AIDS

$\alpha$ -Cyclodextrin sulfate, sodium pentosan polysulfate, and  $\beta$ -cyclodextrin sulfate were evaluated for their inhibitory effect on the replication of human immunodeficiency virus (HIV-1) in normal human peripheral blood mononuclear cells. All three drugs had potent anti-HIV activity,  $\alpha$ -cyclodextrin sulfate being the most potent. The above sulfates were also tested for their direct inhibitory effect on reverse transcriptase in vitro. Pentosan polysulfate inhibited the reverse transcriptase reaction at 4.0  $\mu\text{g ml}^{-1}$  and above, whereas the cyclodextrin sulfates did not. The drugs were not cytotoxic up to 100  $\mu\text{g ml}^{-1}$  and also showed significant lymphoproliferative activities. Pentosan polysulfate and  $\beta$ -cyclodextrin sulfate exhibited higher lymphoproliferative activity than  $\alpha$ -cyclodextrin sulfate. All of the sulfates showed profound antiviral synergism with AZT. An additive anti-HIV effect, rather than a synergistic effect, was observed between the sulfated sugars. Thus, these sulfated sugars, because of their nontoxic nature, lymphoproliferative activity and anti-HIV activity at low concentrations, may be valuable chemotherapeutic agents in the treatment of AIDS. In particular,  $\alpha$ -cyclodextrin sulfate, because of its marked anti-HIV synergism with AZT (which would lower the required dose of AZT in vitro), could result in an efficacious and essentially nontoxic combination chemotherapy for AIDS.



## Molecular Physiology and Genetics Section

### Regulation of calcium mobilization during aging

We have continued to elucidate the mechanisms by which alpha-adrenergic and muscarinic cholinergic regulation of rat parotid cell secretion are altered during aging. Most recent data suggest that although both signal transduction pathways require  $IP_3$  dependent calcium mobilization, different G proteins and/or phospholipase C isoenzymes may be utilized. Alpha-adrenergic stimulated calcium mobilization is preferentially decreased during aging and since neither  $IP_3$  nor alpha adrenergic receptors are lost, the deficit must be intermediate in the signal transduction sequence. In fact, our newest results indicate a close relationship between stimulated  $IP_3$  production and calcium mobilization and a corresponding decrease in both during aging. No changes in the activities or quantities of G proteins or phospholipase C are detected. However, preliminary data suggest that the ability of GTP to shift alpha-adrenergic receptors to the low affinity form (uncoupling of the G protein alpha subunit to activate phospholipase C) is impaired in aged parotid cell membranes. Similar observations have been made in various brain regions (see also our report on muscarinic control of striatal dopamine release), suggesting that this phenomenon may occur frequently during aging of  $IP_3$ /calcium dependent systems.

### The Striatum and Second Messenger Function in Senescence

We are using striatal slices obtained from 6 and 24 mo animals to determine: (a) the interrelationships between the dopaminergic and cholinergic systems (b) the integrity of the dopamine and muscarinic cholinergic receptor-effector systems (c) the regulation of the second messenger systems involved in muscarinic functioning. One mechanism of controlling striatal DA release is through striatal presynaptic cholinergic heteroreceptors presumably located on the same terminals as the DA autoreceptors (possibly  $D_2$  receptors located on interneurons).

In experiments carried out this year we have begun to explore possible age related changes in each step in this signal transduction process. The results are briefly summarized below:

1. No age related differences were seen in NaF (which stimulated phospholipase C thorough G-protein activation) enhancement of  $K^+$ -evoked release of DA or  $IP_3$  production in striatal slices. No age-related differences were seen in Western blot analyses of  $G_o$ ,  $G_\alpha$ ,  $G_{11\alpha}$ , and  $G_{12\alpha}$  or common  $G_\alpha$ .
2. There were age-related differences in the efficacy of the non-hydrolyzable analog of GTP, GppNHP to uncouple the receptor-G-protein complex. In a competitive binding assay using [ $^3H$ ]-QNB and carbachol in the presence or absence of GppNHP, results showed an uncoupling of the receptor-G-protein complex in hippocampal homogenates from the young animals (as indicated by downward shifts in the proportion of the high affinity muscarinic sites) but not in the hippocampal tissue from old animals. This particular assay is sensitive for  $m_1$  and  $m_2$  muscarinic receptor subtypes. A subsequent study using



[<sup>3</sup>H] OXO-M, (which is selective for the high affinity m<sub>2</sub> site) in the presence or absence of GppNHp indicated no age-related differences in receptor-G-protein uncoupling. These findings indicate that the age-related deficits in receptor-G-protein uncoupling may occur in the m<sub>1</sub> receptor subtype and not in the m<sub>2</sub>. We are presently examining these possibilities in both hippocampal and striatal tissue. One working hypothesis is that the deficit in m<sub>1</sub> receptors may involve both coupling and concentration while that of the m<sub>2</sub> may be more involved with concentration (see below).

3. [<sup>3</sup>H]-QNB binding analyses and determinations of muscarinic enhancement of K<sup>+</sup>-evoked DA release were carried out in striata from the same animals (one striatum for each determination). The results indicated that there were decreases in the concentrations of muscarinic receptors in the striata of aged rats and that these decreases were correlated with deficits in muscarinic enhancement of K<sup>+</sup> evoked DA release, especially with the concentration of the M<sub>2</sub>-receptor subtype. Subsequent experiments carried out in this regard also indicated that there were no membrane shifts in the overall distribution of the muscarinic receptors.

The findings from all of these studies suggest that the muscarinic receptor system is somehow altered in aging such that agonist stimulation is no longer effective.

#### Effects of Aging on Sensori-Motor Performance in Rodents

Using an automated image analysis system, we have developed a new psychomotor battery consisting of open field, tightrope, inclined screen, balance beam, rotarod, swim distance and vigor. In all but the open field test, we have introduced an aspect of escape from water (e.g., the mouse must stay on the rotarod to avoid falling into water). In preliminary tests comparing 6- to 24-mo old mice and 27- to 30-mo old mice, the battery proved to be very age-sensitive. In collaboration with Drs. Joseph, Gupta, and Wiener, we have administered deprenyl, a monoamine oxidase inhibitor that has been used successfully in the treatment of Parkinson's disease, in the drinking water of 18-mo old and 27-mo old male C57BL/6J mice and observed these mice in this battery of motor tests at later ages. No evidence of toxicity was noted as the treated mice exhibited normal fluid intake and body weights. Analysis of monoamine oxidase-B activity indicated significant reduction of enzyme activity as early as 3 weeks after initiation of treatment and maintenance of reduced levels over a 9-mo interval. Among mice treated with deprenyl from 18-mo to 24-mo of age, no significant deprenyl effects were observed in any psychomotor parameter except in the rotarod test in which mice treated with 1 mg/kg of deprenyl daily maintained their maximum running speed over 9-mo compared to the age-related decline observed in the other groups. Among mice treated with deprenyl (1 mg/Kg daily) from 27 to 30 mo of age, performance was improved only in the tightrope test, but survival was enhanced by the treatment compared to controls.



### Effects of Aging on Learning/Memory Function in Rodents

After well establishing the involvement of the septo-hippocampal cholinergic system in accurate performance in the 14-unit T-maze, we have expanded our lesion work in young animals to assess the involvement of neocortical regions in maze learning. To this end in collaboration with Drs. Pontecorvo and Jones, we have developed a focal ischemia model in which a photosensitive dye (rose bengal) is injected. When illuminated in a stereotaxically accurate location through the skull, the dye causes multiple thrombi via an oxygen-radical induced platelet aggregation to provide a very specific lesion in the neocortex. Extensive damage to the parietal cortex in male F-344 rats produced marked deficits in maze learning.

In collaboration with Dr. Ordry, another stroke model has been used to create hippocampal lesions. The 4-vessel occlusion (4VO) model in which the carotid arteries are clamped following cauterization of cerebral arteries produces specific lesions to the CA1 region of hippocampus when reperfusion is permitted 15 min after occlusion. Moderate damage to CA1 resulted in impaired maze learning in young (3 mo) male Sprague-Dawley rats. Results from both stroke models further bolster the involvement of the parieto-hippocampal region in maze learning.

### Age-Dependent Expression of Mouse Satellite DNA Sequences in Heart Tissue

Mouse satellite DNA consists of highly repetitive tandem sequences located in the centromeric heterochromatin. It is generally assumed that these simple sequences are not transcribed. We have analyzed total cellular RNA preparations from mouse liver, kidney, brain, and heart tissues at different ages for satellite transcripts. Using recombinant probes containing the major mouse satellite sequence, satellite transcripts were detected only in the heart RNA samples. These transcripts were not detected in the heart muscle of young adult animals (2 and 6 months), but then appeared at the age of 12 months and continued to increase over two-fold up to the age of 32 months. The transcripts were resistant to DNase I and sensitive to RNases and alkaline treatment. Northern hybridization experiments showed a large and heterogenous size range of satellite transcripts. Control studies using short-interspersed (B1 and B2) and long-interspersed (L1 and IAP) repetitive DNA sequence probes did not show a similar age-related pattern of transcription. These results indicate that satellite transcription does occur in mice but is highly tissue and age specific. The unique occurrence of satellite transcription only in adult and senescent heart tissue indicates age to be an important determinant of gene activity. An understanding of the regulatory mechanisms involved could lead to new insights in the biological role of satellite DNA, gene depression of reiterated DNA sequences and the aging process of cardiac muscle.

### Assessment of Primate Aging: Effects of Caloric Modification

This study was designed to determine the effect of diet restriction on the non-human primate. In the third year of the study, rates of body weight gain continue to be substantially reduced in both rhesus and squirrel monkeys





although skeletal growth appears to be unaffected. Absolute food intake is concomitantly reduced in the dietary restricted animals. However, in the past year the food allotment for both control and restricted rhesus monkeys of the aged group was reduced to compensate for decreased appetite.

We continue to observe cross sectional age differences in many parameters including serum alkaline phosphatase, BUN, phosphorous, calcium and thymocyte mitogenesis. In the past year we have also assessed serum dehydroepiandrosterone (DHEA) and DHEA sulfate levels. A greater than 70% reduction occurs for both control and restricted rhesus monkeys. In contrast, squirrel monkeys actually exhibit an increase of more than 2 fold over the age rang studied. These observations will be repeated in one or two years for purposes of confirmation and possible detection of longitudinal changes. For the first time we may now be observing effects of reduced feeding on the age related reduction in serum alkaline phosphatase in Rhesus monkeys and the entrance into puberty (elevation of testosterone levels) of juvenile animals of both species. These represent the first longitudinal changes of sufficient magnitude as to be detectable and will be followed closely in the next year.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00044-17 LCMB

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Metals and Proteins on Nucleic Acids, Information Transfer and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Gunther L. Eichhorn  
Others: Richard B. Beal  
James J. Butzow  
Peter P. Chuknyisky  
Patricia Clark

Chief, LCMB IBS LCMB NIA  
IRTA Fellow IBS LCMB NIA  
Commissioned Officer IBS LCMB NIA  
Sr. Staff Fellow IBS LCMB NIA  
Research Chemist IBS LCMB NIA

COOPERATING UNITS (if any)

Wichita State Univ. (R.P. Singhal); Univ. of Western Ontario (S.J. Karlik); Univ. of Toronto (U. DeBoni); Israel Institute for Biological Research (D. Waysbort)

LAB/BRANCH

Laboratory of Cellular and Molecular Biology

SECTION

Inorganic Biochemistry Section

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

6.8

PROFESSIONAL:

4.8

OTHER:

2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they impact on the information in such a way as to influence biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) the mechanism of involvement of aluminum in Alzheimer's disease; (3) crosslinking of nucleic acid strands by metal ions; (4) the structure of the active site of RNA polymerase; (5) metal ions and cellular aging.



<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE</b> <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 AG 00133-8 LCMB						
PERIOD COVERED <u>October 1, 1989 to September 30, 1990</u>								
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <u>In Vivo NMR Studies of Aging in Cells and Animals</u>								
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">PI: Gunther L. Eichhorn</td> <td style="width: 33%;">Chief, LCMB</td> <td style="width: 33%;">IBS LCMB NIA</td> </tr> <tr> <td>Others: Richard B. Beal</td> <td>IRTA Fellow</td> <td>IBS LCMB NIA</td> </tr> </table>			PI: Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA	Others: Richard B. Beal	IRTA Fellow	IBS LCMB NIA
PI: Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA						
Others: Richard B. Beal	IRTA Fellow	IBS LCMB NIA						
COOPERATING UNITS (if any) Cardiovascular Section, Clinical Physiology Branch, National Institute on Aging; Department of Radiology, Johns Hopkins University (J.L. Fleg)								
LAB/BRANCH <u>Laboratory of Cellular and Molecular Biology</u>								
SECTION <u>Inorganic Biochemistry Section</u>								
INSTITUTE AND LOCATION <u>National Institute on Aging, NIH, Baltimore, Maryland 21224</u>								
TOTAL MAN-YEARS: 0.4	PROFESSIONAL: 0.4	OTHER: 0						
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews								
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  <p>NMR Spectroscopy is used to study the metabolic changes associated with exercise in the flexor muscle of the forearm of human volunteers. Isometric exercise at variable workloads as well as constant workload are carried out using a hand dynamometer which is interfaced to a personal computer and a display unit. Changes in phosphocreatine (PCr) and inorganic phosphate (<math>P_i</math>) as well as intracellular pH are monitored via <math>^{31}P</math> NMR spectroscopy during the exercise. Age-related differences in these parameters during exercise are studied in subjects of the BLSA using these protocols.</p>								

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LOS-IRP-NIA



<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE</b> <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 AG 00046-20 LCMB
PERIOD COVERED October 1, 1989 to September 30, 1990		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Molecular Recognition of Lipids and Lipophiles by Cyclodextrin Derivatives</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)		
PI: Josef Pitha Others: J. Torres-Labandeira DOD 05/29/90 C. Trinadha Rao EOD 10/27/87 Yan Xia DOD 07/22/90	Section Chief Visiting Fellow Visiting Fellow Visiting Fellow	MCS LCMB NIA MCS LCMB NIA MCS LCMB NIA MCS LCMB NIA
COOPERATING UNITS (if any) Bengt Lindberg (Univ. of Stockholm, Sweden); George Taylor (Univ. of Missouri-St. Louis); Rita Anand (NIH); Stephen Baker (Univ. of Florida); Daniel Armstrong (Univ. of Missouri-Rolla); Kaneto Uekama (Kumamoto Univ., Japan)		
LAB/BRANCH Laboratory of Cellular and Molecular Biology		
SECTION Macromolecular Chemistry Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224		
TOTAL MAN-YEARS: 3.5	PROFESSIONAL: 3.5	OTHER: 0
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Cyclodextrins are conversion products of starch and when suitable chemically modified represent potent solubilizers of lipophiles. In the chemical part of the project the rules for chemical modification of cyclodextrins were established. In the biomedical part of the project (a) hydroxypropylcyclottrins were used to study the effects of supplementation of adrenal and sex hormones in rats and (b) cyclodextrin sulfates were found to inhibit replication of HIV1.		

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00047-20 LCMB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structure-Function Relationships in Hemoglobin and Erythrocytes

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Joseph M. Rifkind	Chief, MDS	MDS LCMB NIA
Others:	Abraham Levy	Sr. Staff Fellow	MDS LCMB NIA
	Lu Zhang (DOD 11/09/89)	Visiting Fellow	MDS LCMB NIA
	Omoefe Abugo (EOD 04/23/90)	Visiting Fellow	MDS LCMB NIA

COOPERATING UNITS (if any) NIA/LCS/CFS (E. Lakatta); LMC/NCI (F. Friedman); Indian Inst. of Tech., Madras, India (P.T. Manoharan); Univ. CA-San Diego, La Jolla CA (V.S. Sharma); Letterman Army Inst. of Research, San Francisco CA (R. Winslow); Benedict College, Columbia SC (K. Alston); Waldenberg Center for Gerontological Studies (D. Danon)

## LAB/BRANCH

Laboratory of Cellular and Molecular Biology

## SECTION

Molecular Dynamics Section

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.7

## PROFESSIONAL:

2.7

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects    ☒ (b) Human tissues    ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project focuses on the mechanism involved in regulating the binding of oxygen to hemoglobin and the transport of oxygen to the tissues. Emphasis is placed on ways in which these functions are impaired and change with age. These studies have focused on the oxidation of hemoglobin, which produces nonfunctional hemoglobin and the simultaneous release of oxyl radicals. The enhancement of these oxidative processes under hypoxic conditions is being explored as a possible source of tissue and organ damage, which would be exacerbated during aging. Studies are also included which are directed at the stability of the entire erythrocyte and the erythrocyte membrane.

LMG-IRP-NIA

IN-IRP-NIA

LCP-IRP-NIA

LCS-IRP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00301-7 LCMB

PERIOD COVERED October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: I. Hormone and Neurotransmitter Action.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: G.S. Roth, Chief, Molecular Physiology and Genetics Section, LCMB, NIA

Others:

B. Baum

A. Miyamoto

M. Blackman

## COOPERATING UNITS (if any)

Patient Care Branch, National Institute of Dental Research, Clinical Physiology Branch

## LAB/BRANCH

Gerontology Research Center,

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.3

## PROFESSIONAL:

1.3

## OTHER:

2.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is mainly involved in elucidating those mechanisms by which the ability of hormones and neurotransmitters to regulate physiological functions is altered during aging.

LMG-IRP-NIA

IN-IRP-NIA

LCP-IRP-NIA

LCS-IRP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00306-2 LCMB

PERIOD COVERED October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological

Functions During Aging: II. Central Nervous System Responsiveness

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J.A. Joseph, Research Pharmacologist, Molecular Physiology and Genetics  
Section LCMB, NIA, G.S. Roth, Chief, MPGS, LCMB, NIA

## Others:

Dr. E. Mesco	IRTA	LCMB, NIA
Dr. Keiji Yamagami	Visiting Scientist	LCMB, NIA
Dr. D.K. Ingram	Research Psychologist	LCMB, NIA
Dr. M. Blake	Staff Fellow	LMG, NIA
Dr. N. Appel	Staff Fellow	NIDA

COOPERATING UNITS (if any)

None

LAB/BRANCH

Gerontology Research Center

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

3.0

PROFESSIONAL:

2.5

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects    ☐ (b) Human tissues    ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project attempts to understand those mechanisms involved in age related changes in central nervous system responsiveness.

LMG-IRP-NIA

LN-IRP-NIA

LCP-IRP-NIA

LOS-IRP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

PERIOD COVERED October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: III. Behavioral Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Donald K. Ingram, Research Psychologist MPGS, LCMB, NIA

Others:

E. Bresnahan

D. Danon

B. Davis

P. Garofalo

M. Gupta

C. Hohmann

B. Jones

J. Joseph

M. Jucker

H. Kametani

H. Kleinman

J. Knapka

S. Kobayashi

M. Ord

M. Pontecorvo

G.S. Roth

E. Spangler

H. Wiener

L. Williams

COOPERATING UNITS (if any)

(see below)

LAB/BRANCH

Gerontology Research Center

SECTION

Molecular Physiology and Genetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

5.3

PROFESSIONAL:

3.0

OTHER:

2.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The purpose of this project is to assess the effects of aging at a behavioral level of analysis in animal models, to identify neurobiological mechanisms associated with these effects, and to test interventions which might alter age-related performance decrements. Rodent models are tested in a battery of sensori-motor and learning/memory tasks. Neurochemical and neurohistological assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, various pharmacologic treatments, and neural tissue grafting. Multiple genotypes are examined to determine possible genetic involvement in the pattern of age-related behavioral impairment.

COOPERATING UNITS

Essex Community College, (E. Bresnahan); Neuroanatomy Lab U. Rochester Sch. Med. (B. Davis); U. Louisville Sch. of Med. (M. Gupta); Tokyo Metropolitan Institute of Gerontology (S. Kobayashi); St. John's University (H. Wiener); Nat'l Inst Dental Res. (H. Kleinman); Pennwalt Corp. (M. Ord); Upjohn Company (L. Williams); JHU Medical School (C. Hohmann); LSU School of Med (D. Danon); Nat. Ctr. Res. Resources (J. Knapka)





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG-00303-7 LCMB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Physiological

Functions During Aging: IV Gene Expression and the Biology of Human Longevity

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Richard G. Cutler

Research Chemist

LCMB, NIA

## Others:

D.K. Ingram

G.S. Roth

M. Simic

D. Bergtold

A. Ayala

H. Alessio

A.H. Goldfarb

J. Vijg

A. Brower

A.S. Khan

J.W. Gaubatz

## COOPERATING UNITS (if any)

NIH, NIAID (A.S. Khan); NBS (M. Simic &amp; D. Bergtold); TNO (J. Vijg &amp; A. Brower),

## LAB/BRANCH

Gerontology Research Center

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.0

## PROFESSIONAL:

2.0

## OTHER:

0.0

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The objective of our research program is to search for unique characteristics of human biology which determine their extraordinary capacity for general health maintenance and longevity as compared to all other mammalian species. This research program has been guided by theoretical studies suggesting that a common set of specific longevity determinant processes exists in all mammals. Work has centered on two basic but interrelated questions: (1) is the cause of aging largely the result of dysdifferentiative processes and (2) is the rate of aging governed by mechanisms acting to stabilize the proper differentiated state of cells? With reference to the first question, stability of gene regulation has been investigated by measuring the steady state levels of mRNA for the genes coding for the endogenous retroviruses (human 4-1, mouse MuLV), oncogene (c-myc) and satellite heterochromatin DNA as a function of age in a number of tissues from mice and human. Recent studies of the possible age-dependent expression of mouse satellite DNA sequences show that (1) such DNA sequences do become expressed in mammalian species, (2) such expression is highly tissue-specific, being found only in heart tissue in C57BL/6J mice, and (3) expression is correlated with age of the mice, increasing in a linear manner through life span. Expression of human 4-1 endogenous retrovirus in liver and kidney tissues have now been confirmed using in situ hybridization studies. Expression in both tissues is highly localized within hot-spot clusters of cells.

117  
1904  
2000

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00304-4 LCMB

## PERIOD COVERED

October 1, 1989 to September 30, 1990

Regulation of Physiological  
Functions During Aging: V.

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Assessment of Primate Aging: Effects of Caloric Modification

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: G.S. Roth	Chief, MPGS	LCMB, NIA
D.K. Ingram	Research Psychologist, MPGS	LCMB, NIA
R.G. Cutler	Research Chemist, MPGS	LCMB, NIA

Others: R. Weindruch, H.S.A., NIA; J. Knapka, Animal Center Section,  
M. Blackman, LCP, NIA; W. Ershler, U. Wisconsin, Madison, WI; W. Wood,  
H. Armbrrecht, R. Strong, V.A.M.C., St. Louis, Mo; J. Conway, U.S.D.A.,  
Beltsville, Md; D. Danon, Weizmann Inst., Rehovot, Israel; D. Jarrel, S. Judge,  
Animal Center Section, DRS.

## COOPERATING UNITS (if any)

Dept. of Med. Univ. of Wisc., Madison, WI

## LAB/BRANCH

Gerontology Research Center

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

2.0

## OTHER:

2.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project is attempting to determine whether caloric modification of the diets of Rhesus and squirrel monkeys can affect aging rate as assessed by various physiological, biochemical and behavioral indices.



LNG-IRP-NIA

LN-IRP-NIA

LCP-IRP-NIA

LCS-IRP-NIA



## Clinical Immunology Section

The main program areas in the Section are:

- A) Lymphocyte Activation Pathways
- B) AIDS
- C) Clinical Immunology

### A) Lymphocyte Activation - Summary

Further evidence has been obtained that certain of the activation pathways in T cells from elderly humans are not functional. The deficiency appears related to the state of cell differentiation and the expression of the antigen receptor complex.

Activation pathways that proceed through the cdc-2 gene product, a kinase which dephosphorylates tyrosine residues, show cell cycle specificity, also, the activity of the cdc-2 kinase is related to the stimulatory activity of IL-2 and is tied in to the phosphorylation of the H-1 histone protein.

### B) Clinical Immunology - Summary

The determination of the level of T cell activation can be accomplished by measuring the quantity of soluble IL-2 receptor in the serum or CSF. This seems to be a reliable indicator of the degree of inflammation and T cell involvement. IL-2R levels are elevated in the CSF of multiple sclerosis patients and in patients with metastatic leukemic tumors of the CNS.

The use of multiple routes of immunization, both live attenuated or killed virus, multivalent vaccine preparations, and both primary and booster immunizations can result in protective levels of anti influenza antibodies in a nursing home population.

### C) AIDS

HIV infections in individuals over 40 years of age progress to AIDS in half the period of time as seen with younger patients. An investigation of this feature of an HIV infection in infected individuals over 60 years of age showed that antibody responses to the virus were less well developed and T cell losses more severe in the older group.





DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-AG-00104-14-LCP

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Immune Survey of the Longitudinal Project Participants\*

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: W. H. Adler Medical Officer, PHS LCP, NIA  
Others: +J. E. Nagel Medical Officer, PHS LCP, NIA  
L. Song Visiting Fellow LCP, NIA EOD 9/89  
R. K. Chopra Visiting Fellow LCP, NIA left 11/89  
J. J. Proust Guest Worker LCP, NIA left 4/90  
S. K. Kittur Medical Staff Fellow LCP, NIA left 7/90  
D. C. Powers Medical Staff Fellow LCP, NIA left 7/90

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Clinical Immunology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland

TOTAL MAN-YEARS:

3.0

PROFESSIONAL:

1.8

OTHER:

1.2

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

These studies utilize participants in the Baltimore Longitudinal Study of Aging to gain insight into the genetic, biochemical and molecular mechanisms underlying age-associated changes in immune function. The projects are directed toward distinguishing and characterizing the origins of defective T cell activation and proliferation.

Others: +F. J. Chrest Biologist LCP, NIA  
G. C. Collins Biologist LCP, NIA  
R. S. Pyle Bio. Lab. Tech LCP, NIA  
B. A. Dorsey Bio. Lab. Tech. LCP, NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00095-17-LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Role of Cell Membrane Structures on Cellular Recognition

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: W. H. Adler Medical Officer, PHS LCP, NIA

Others: +J. E. Nagel Medical Officer, PHS LCP, NIA  
 S. D. Kittur Medical Staff Fellow LCP, NIA left 7/90  
 D. C. Powers Medical Staff Fellow LCP, NIA left 7/90

## COOPERATING UNITS (if any)

Drs. R. Winchurch, D. Kittur and S. Xu - Dept. of Surgery, FSK  
 Medical Center, Johns Hopkins University, Baltimore, MD, Dr. Rajesh  
 Chopra, School of Hygiene, Johns Hopkins University, Baltimore, MD

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.25

## PROFESSIONAL:

1.45

## OTHER:

.8

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Activation of T cells results in the release of Interleukin-2 and the expression of the Interleukin-2 receptor. In humans there are at least two chains that comprise this receptor. In rats there are 4 proteins which can bind IL-2 and together they form the high affinity receptor necessary for the transmission of the IL-2 growth signal. The IL-2 receptor ( $\alpha$  chain) can be found in soluble form in activated T cell culture supernates, and in serum and CSF from patients with infectious and inflammatory illness. The CSF IL-2R levels are significantly elevated in patients with multiple sclerosis. Influenza vaccine studies have shown additive effects on antibody production with the use of combined parenteral and nasal immunization with killed and live attenuated influenza vaccines.

Others: F. J. Chrest Biologist LCP, NIA  
 R. S. Pyle Bio. Lab Tech. LCP, NIA  
 B. A. Dorsey Bio. Lab Tech LCP, NIA  
 G. D. Collins Biologist LCP, NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00093-18-LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Basis of Regulation of the Humoral Immune Response

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	A.A. Nordin	Research Chemist	LCP, NIA
Others:	J.J. Proust	NIH Special Volunteer	LCP, NIA left 4/90
	Y. Kim	Visiting Fellow	LCP, NIA EOD 10/89
	M.A. Buchholz	Biologist	LCP, NIA
	F.J. Chrest	Biologist	LCP, NIA

## COOPERATING UNITS (if any)

J. Shaper and N. Shaper, Oncology Department, Johns Hopkins University, Baltimore, Maryland

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.7

## PROFESSIONAL:

2.5

## OTHER:

1.2

## CHECK APPROPRIATE BOX(ES)

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |   |
| <input type="checkbox"/> (a2) Interviews    |  |   |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The activation and proliferation of T lymphocytes was studied in vitro to investigate the biochemical events associated with signals transmitted through specific membrane receptors. The expression of the cell cycle regulating kinase, cdc2, is linked to the T cell receptor on resting murine T lymphocytes. By the late G<sub>1</sub> phase, the kinase protein is detectable but does not express enzymatic activity until the cells reach premetaphase. As in other cell systems, this kinase activity is associated with the dephosphorylation of tyrosine residues within the cdc2 protein and one of the targets for phosphorylation is H1 histone.

The proliferation of T lymphocytes as regulated by the interaction of IL-2 with its' specific receptor involves the phosphorylation state of tyrosine residues in a series of proteins. Withdrawal of IL-2 from a dependent T cell line results in apoptosis and the dephosphorylation of tyrosine residues in four distinct proteins but no apparent change in the phosphorylation state of cdc2. The IL-2 starved cells showed an unexpected significant increase in cdc2 specific mRNA, high levels of both H1 histone and casein kinase and accumulated in mitosis. The addition of IL-2 returns the starved cells to a normal proliferative cycle and re-establishes the phosphorylation of the tyrosine residues of the affected proteins.

In vivo experiments to demonstrate the effect of IL-2 as an immunoadjuvant with classical influenza vaccination of old mice showed a very striking increase in serum antibody titer. The most striking observation was that the secondary response to the influenza vaccine was significantly enhanced irrespective of the presence of rIL-2 in the initial injection.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00096-17-LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Lymphocyte Activation and Function in Aging Individuals

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M. A. Brock Research Biologist LCP, NIA

Others: W. H. Adler Medical Officer, PHS LCP, NIA

F. J. Chrest Biologist LCP, NIA

## COOPERATING UNITS (if any)

H. J. Hoffman, Biometry Branch, NICHD

## LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.3

## PROFESSIONAL:

1.1

## OTHER:

.2

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cellular activation after ligand-receptor interactions includes rapid polymerization of actin, and, in T lymphocytes, the concomitant lateral redistribution of surface receptors and of cytoskeletal actin. Cytochalasin E specifically depolymerizes filamentous actin (F-actin), and it increased proliferation of resting T cells from old but not young mice. This suggested an age-related increase in F-actin which could impair lymphocyte functions.

The F-actin content of resting ( $G_0$ ) and stimulated T lymphocytes from spleens of C57BL/6 mice was quantitated using a fluorescein-like fluorophore, Bodipy, conjugated to phalloidin which binds only to F-actin. Flow cytometric analysis showed that baseline levels of relative F-actin content were significantly increased in resting cells from aged mice (24-25 mo). Activation of  $G_0$  T lymphocytes with Concanavalin A produced an immediate (within 60 sec.) increase in F-actin in cells from old mice and it returned to baseline levels within 2 min.; no further increase occurred for up to 40 min. In contrast, F-actin levels in cells from young mice (4-6 mo.) began to increase within 2 min. after activation and continued to rise for up to 50 min.

These differences in F-actin content and polymerization kinetics may result in impairment of cytoskeletal functions and be related to the age-associated alterations in signal transduction in T lymphocytes from older individuals.

A comprehensive review of the topic, Chronobiology and Aging, was written. This was requested by the associate editor of the Journal of the American Geriatrics Society.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00261-03-LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Host Factors Relating to HIV Infections

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA
Others: +	J. E. Nagel	Medical Officer, PHS	LCP, NIA
	N. E. Kendig	Medical Officer, PHS	LCP, NIA
	S. D. Kittur	Medical Staff Fellow	LCP, NIA left 7/90

## COOPERATING UNITS (if any)

Dr. Mary Lou Clements, Vaccine Center, Johns Hopkins University,  
 Dr. John Bartlett, Dept. Medicine, Johns Hopkins University,  
 Drs. E. Dax and R. Lange, NIDA.

## LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

4.8

## PROFESSIONAL:

2.2

## OTHER:

2.6

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The vaccinia insert p-160 vaccine can induce anti-160 antibody in all subjects and a cytotoxic T cell response in about 1/3 of the recipients. The anti-160 Ab is able to function in an ADCC assay against HIV infected targets. As an HIV infection progresses there is a decline in the amount of antibody to core proteins but no change in antibody levels to envelope proteins. As a general rule, illicit drugs have the greatest detrimental effect on NK cell function rather than on T or B cell function.

Others:	F. J. Chrest	Biologist	LCP, NIA
	G. D. Collins	Biologist	LCP, NIA
	M. Schoonmaker	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	B. A. Dorsey	Bio. Lab Tech.	LCP, NIA



## Section Summary

The research program of the Endocrinology Section, LCP has the dual objectives of elucidating: (a) the mechanisms by which aging alters hormone secretion and action and; (b) the extent to which hormone changes produce age-associated effects on metabolism, body composition, and physiology. We have concentrated on the effects of aging on regulation of those endocrine systems under the control of the anterior pituitary gland in both animal models and human (clinical) studies.

We are investigating the cellular, biochemical, and molecular mechanisms responsible for age-related alterations in production of luteinizing hormone (LH) and prolactin (PRL) in the Wistar rat. The *in vitro* secretion of LH and PRL by isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perfusion culture systems. Past work revealed that age-related alterations in basal and modulated hormone secretion by pituitary cells from old rats result (in part) from multiple changes in intrinsic pituitary gonadotropic and lactotropic cell functions including; decreased GnRH- and dopamine-mediated membrane signal transduction; decreased transcription of LH- $\beta$ , and presumably  $\alpha$ -subunit, genes; and altered post-transcriptional regulation of PRL secretion.

New findings include (1) the failure to reverse the *in vitro* LH hyposecretion by repetitive perfusion pulses of GnRH, which parallels our prior observations after repetitive *in vivo* administration of GnRH and further suggests that aging is associated with an intrinsic pituitary gonadotropic secretory defect, and (2) age-related decreases in secretion of LH in primary monolayer cultures of heterogeneous pituitary cell suspensions after administration of the phorbol ester, PMA, a protein-kinase C activator as well as after nifedipine, a voltage gated calcium channel blocker. The latter observations suggest that both long and short term stimulation of LH release may proceed through separate mechanisms which are differentially affected by aging.

Current efforts are directed at introducing new methods in our laboratory to investigate (1) the mechanisms responsible for the age-related signal transduction defect in gonadotropic cells. These include centrifugal elutriation of pituitary cell suspensions for enrichment of the gonadotrope cell population, radioimmunoassay of cell membrane G-proteins, HPLC quantification of the various phosphoinositides (PI's) elaborated as second messengers during stimulation of the gonadotropic cells, and measurement of calcium mobilization and calcium currents in stimulated gonadotropic cells, (2) individual cell function, using reverse hemolytic plaque assay to quantitate hormone secretion by gonadotropic and lactotropic cells, as well as immunocytochemistry and immunofluorescence to identify, sort, and count gonadotropic and lactotropic cells, and (3) molecular mechanisms underlying transcriptional and post-transcriptional regulation of LH- $\beta$  and PRL synthesis, respectively.

Normal aging in man is associated with various alterations in hormone secretory physiology and in body composition. However, the interactions among aging, changes in bone, muscle, and fat, and hormonal alterations remain to be clarified. In particular, aging has been reported to be associated with: (1) in women, deficiency of ovarian estrogen, a hormone with important beneficial effects on bone and other metabolic functions, (2) increases in the catabolic hormone, cortisol, and (3) decreases in the anabolic hormones, growth hormone (GH) and insulin-like growth factor I (IGF-I).

We have completed a study of the interaction of age and transdermal estradiol replacement at 3 different doses in 28 postmenopausal women, investigating effects of estrogen before and during progestogen administration on basal GH, GH responses to GHRH, calcium and calciotropic hormone regulation. We found that: (1) Older women remain responsive to the bone-



conserving influence of estrogen as measured by urine calcium excretion, plasma calcium, and levels of parathyroid hormone; and (2) this effect is not mediated via alterations in plasma calcitonin or increased basal GH or IGF-I secretion. Unexpectedly, treatment with transdermal estrogen, unlike oral estrogen, appeared to inhibit the pituitary GH response to GHRH. Because estrogen therapy did not increase GH or calcitonin, we conclude that osteoporotic women may benefit from the addition of GH or calcitonin therapy to estrogen replacement.

A study to quantitate the effects of aging on the regulation of the hypothalamic-pituitary-adrenal axis has also been completed. We studied 11 young and 11 older men by overnight monitoring of adrenal function with 12 hours of every 10-minute blood sampling followed by corticotropin releasing hormone (CRH) stimulation tests under basal conditions. We then studied each man during suppression with 3 different doses of dexamethasone repeated at weekly intervals by 4 hours of every 10-minute blood sampling followed again by CRH stimulation tests. Results showed that both spontaneous and CRH-stimulated secretion of ACTH and cortisol were unchanged with age and responded similarly to suppression with increasing doses of dexamethasone. These findings provide strong evidence against the hypothesis that an age-related loss of sensitivity of the hypothalamic-pituitary-adrenal axis to negative feedback by glucocorticoids leads to glucocorticoid excess and resultant changes in body composition and metabolism.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

ZO1 AG 00023-14 LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging. Hypothalamic-Pituitary Function in Experimental Animals

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Ph.D., Senior Investigator, LCP, NIA

Other:

M. R. Blackman, M.D. Guest Scientist, LCP, NIA

Emiliano Corpas y Cobisa, M.D., Ph.D., Visiting Scientist, LCP, NIA

Marco Piñeyro, BS, M.S., Chemist, LCP, NIA

Robin Roberson, B.S., Chemist, LCP, NIA

George S. Roth, Ph.D., Section Chief, MPGS, LCMB, NIA

David Danner, M.D., Ph.D. Section Chief LMG, NIA

Atsushi Miyamoto, Ph.D., Visiting Scientist, MPGS, LCMB, NIA

David Stewart, M.S. LMG, NIA

Donald K. Ingram, Ph.D. Senior Investigator, MPGS, LCMB, NIA

## COOPERATING UNITS (if any)

Dept. of Medicine, F.S.K. Med. Center and J.H.U. Medical School

Molecular Physiology and Genetics Section, LCMB, GRC

Laboratory of Molecular Genetics, GRC

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Endocrinology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.5

## PROFESSIONAL:

0.8

## OTHER:

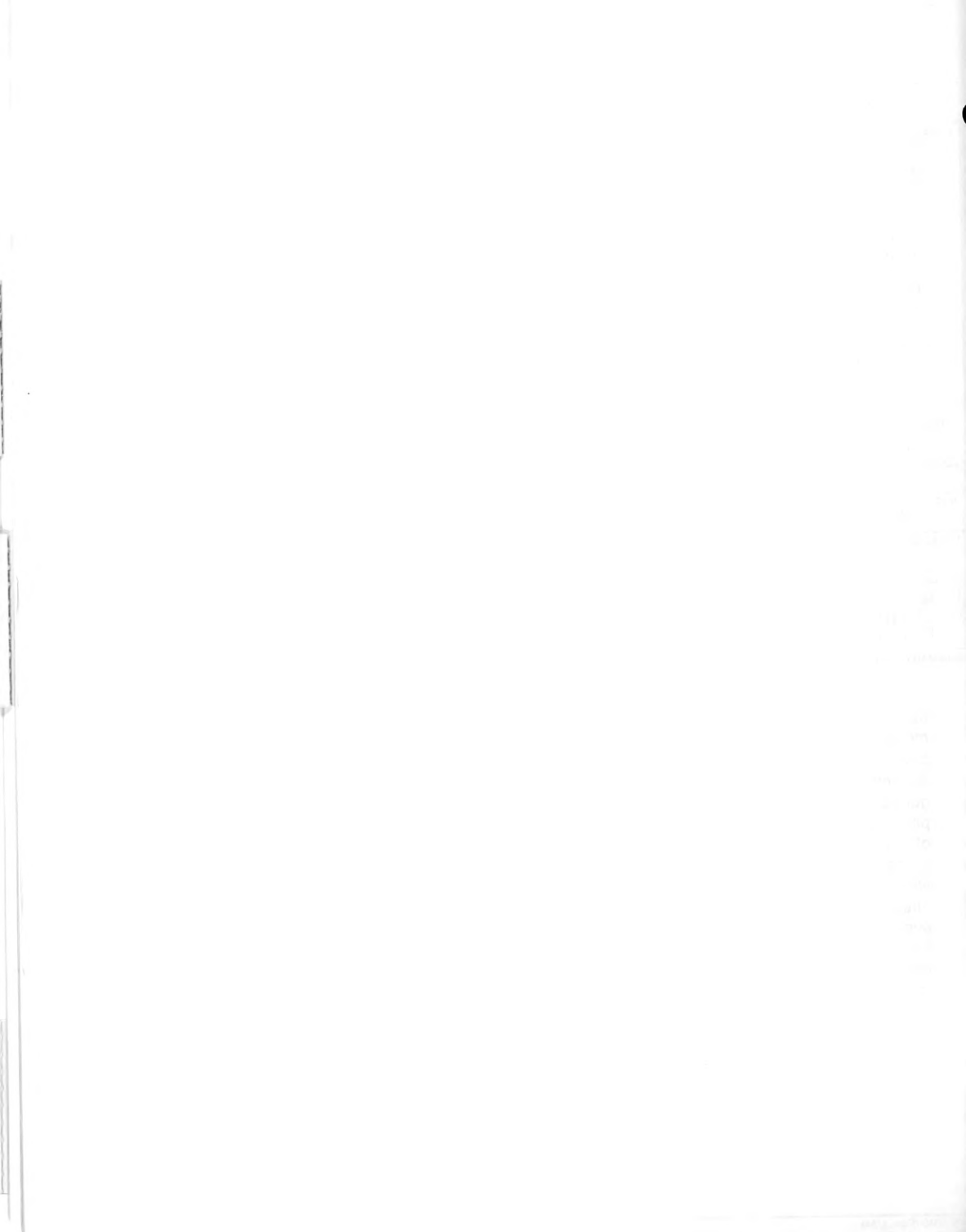
1.7

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Continuing studies of pituitary tissues in the automated perfusion system confirm the observations of an age-related decrease in GnRH-stimulated LH secretion, previously shown in monolayer cultures. The failure to reverse the in vitro LH hyposecretion by repetitive perfusion pulses of GnRH parallels our prior observations after repetitive in vivo administration of GnRH and further suggests that aging is associated with an intrinsic pituitary gonadotropic secretory defect. Recent studies in primary monolayer cultures of heterogeneous pituitary cell suspensions reveal age-related decreases in secretion of LH after administration of the phorbol ester, PMA, a protein-kinase C activator as well as after nifedipine, a voltage gated calcium channel blocker. These observations suggest that both long and short term stimulation of LH release may proceed through separate mechanisms which are differentially affected by aging. Newer techniques for examining the cellular, biochemical, and molecular events responsible for age-related alterations in LH and PRL secretion have been introduced into our laboratory. These include; centrifugal elutriation, reverse hemolytic plaque assay, immunocytochemistry and immunofluorescence, RIA of G-protein subunits, and HPLC measurement of PIP metabolites. The effects of in vitro estrogen stimulation on LH- $\beta$  and PRL gene transcription is being studied in monolayer cultures of pituitary cells from old vs mature female rats.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00013-15 LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones, Hormone Receptors, and Aging. III. Aging and Human Endocrine Regulation

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, LCP, NIA

Other:

Marc R. Blackman, M.D. Guest Scientist, LCP, NIA

Michele Bellantoni, M.D., Medical Staff Fellow LCP, NIA

Claire Waltman, M.D., Medical Staff Fellow LCP, NIA

Emiliano Corpas y Cobisa, M.D., Ph.D., Visiting Scientist, LCP, NIA

William Adler, M.D., Section Chief, IS, LCP, NIA

George P. Chrousos, M.D., Senior Investigator, DEB, NICHD

## COOPERATING UNITS (if any)

Depts. of Medicine, Francis Scott Key Med. Center and J.H.U. Medical School

Immunology Section, LCP

Developmental Endocrinology Branch, NICHD

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Metabolism Section, LCP

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

2.7

## PROFESSIONAL:

2.4

## OTHER:

0.3

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

Continuation of this project in FY-90 has included completion of a study of the interaction of age and transdermal estradiol replacement at 3 different doses in 28 postmenopausal women, investigating effects of estrogen with and without progestogen on basal growth hormone (GH) and IGF-I, GH responses to GHRH, as well as calcitropic and gonadotropic hormone regulation. We found: (1) older women remain responsive to the bone-conserving action of estrogen; and (2) estrogens' action to preserve bone mass appears to be independent of any modulation of GH, IGF-I, or calcitonin secretion. A study to quantitate the effects of aging on the regulation of the hypothalamic-pituitary-adrenal axis has also been completed in 11 young and 11 older men, using overnight monitoring of pituitary-adrenal function with 12 hours of every 10-minute blood samples followed by CRH stimulation tests under basal conditions and then 4 hours of every 10-minute blood sampling followed by CRH stimulation tests repeated at weekly intervals during ACTH suppression with each of 3 doses of dexamethasone. Results showed that both spontaneous and CRH-stimulated secretion of ACTH and cortisol were unchanged with age and responded similarly to suppression with graded doses of dexamethasone. These findings provide strong evidence against the hypothesis that an age-related loss of sensitivity of the hypothalamic-pituitary-adrenal axis to negative feedback by glucocorticoids leads to glucocorticoid excess and resultant changes in body composition and metabolism. A new study using 24 hr. monitoring of spontaneous pulsatile GH secretion, acute GH response to iv GHRH, and plasma IGF-I measurements, all done before after two weeks of chronic GHRH injections repeated at 2 different doses, has been initiated in order to investigate the relationship of GH deficiency to aging and to test the effectiveness of possible interventions for raising GH and IGF-I secretion in older people.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00021-27 LCP

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Study of Normal Human Variability and Cross Cultural Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.C. Plato	Sr. Research Geneticist	LCP NIA
J.D. Tobin	Chief, Applied Physiology	LCP NIA

COOPERATING UNITS (if any)

CNS NINDS; CPSB NCI; University of Maryland; University of Zagreb, Yugoslavia;  
Indiana University.

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS

0.20

PROFESSIONAL:

0.15

OTHER

0.05

CHECK APPROPRIATE BOX(ES)

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|--|--|--------------------------------------|
| <input checked="" type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors                   |  |                                      |
| <input checked="" type="checkbox"/> (a2) Interviews    |  |                                      |

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project represents an ongoing collaborative effort, involving WHO and other national and international laboratories to coordinate the collection, evaluation and interpretation of normal genetic markers in order to study the cross-cultural patterns of genetic and extraneous factors as they relate to normative aging and to diseases with late onset, including Alzheimer's disease, breast cancer, Amyotrophic Lateral Sclerosis, and Parkinsonism Dementia. Specifically, the objectives of this study are: A) To study the cross cultural patterns of genetic and non-genetic factors in an effort to better understand the process of normative aging. B) To study the genetic segregation of these markers in families with late onset diseases, such as Alzheimer's disease, breast cancer, ALS and others, in an effort to establish genetic linkages and eventual identification of the factors responsible for these diseases. C) To study the distribution of dermatoglyphics, lateral dominance and other genetic variables in BLSA participants and other control samples, as well as in patients with late onset diseases.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00022-14 LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders )

Bone Loss with Age: Epidemiological, Familial and Cross-Cultural Considerations

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator ) (Name, title, laboratory, and institute affiliation)

C.C. Plato, Ph.D. Sr. Research Geneticist LCP NIA

J.D. Tobin, M.D. Chief, Applied Physiology LCP NIA

T.A. Roy, M.A. Biologist LCP NIA

S.S. Sherman, Ph.D. IRTA Fellow LCP NIA

## COOPERATING UNITS (if any)

University Zagreb, Yugoslavia; Nihon University, Tokyo; University of Maryland;  
Francis Scott Key Medical Ctr.; Johns Hopkins University; CNS, NINDS

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Applied Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS

2.25

## PROFESSIONAL

1.05

## OTHER

1.20

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

At some time during the fourth decade of life, the human skeleton begins to lose bone. That is, bone mass decreases in relation to bone volume. Menopause and the associated estrogen deficiency will enhance bone loss in females. It has also been suspected that bone loss is familial, mainly because of the increased prevalence of osteoporosis in relatives, although there are no satisfactory scientific data to support either a familial or a genetic control of bone loss. In long bones, cortical bone is resorbed from the endosteal surface. Because of the thinning of the cortical bone shell, bones lose their mechanical integrity and fracture more readily. The trabecular bone mass of the vertebral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and become more vulnerable to vertebral collapse. Vertebral compression fractures and fractures of the femoral neck are the most serious consequences of bone loss.

This project deals with the epidemiological, genetic, cross-sectional, longitudinal, and biomechanical aspects of bone loss (1) among the participants of the Baltimore Longitudinal Study of Aging (BLSA), in osteoporotic patients (2) in genetic isolates of the Croatian Islands of Yugoslavia and the island of Guam in Micronesia, (3) senior athlete population, (4) in long distance runners and relatively inactive normal controls, and, (5) in rats and other animals.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00028-14 LCP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less Title must fit on one line between the borders.)

Epidemiological and Genetics Studies of ALS/PD Complex of Guam

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

## Principal Investigators

C.C. Plato Sr. Research Geneticist LCP NIA

J.D. Tobin Chief, Applied Physiology LCP NIA

## Other Investigators:

R.C. Elston Louisiana State University

J. Bailey-Wilson Louisiana State University

## COOPERATING UNITS (if any)

D.C. Gajdusek, Chief, CNS NINDS, R.M. Garruto, Sr. Staff Associate, CNS NINDS

R.T. Yanagihara, Research Associate, CNS NINDS

L.T. Kurland, Chief, Epidemiology Branch, Mayo Clinic

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Applied Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS

.20

## PROFESSIONAL

0.15

## OTHER

0.05

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project represents further efforts to elucidate the etiology of high incidence of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) on the island of Guam. A patient-control prospective study (Registry) was established in 1958. The initial analysis of the Registry data published in 1967 and the follow up analysis published in 1986 showed that these diseases as found on Guam are highly familial. That is, relatives of patients have a higher risk for developing the disease than those of controls. The next question to be answered is whether this familial occurrence is due to genetic or environmental factors. The specific objectives of this study are:

A) To ascertain the extent of genetic involvement in the high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia through: (1) segregation analysis of the pedigrees of all patients diagnosed since 1958 and, (2) through segregation analysis of sibships where both parents, one parent or neither of the parents (controls) are affected with ALS and PD.

B) To study the distribution of various established genetic and anthropological markers among the normal Guamanian populations and compare them with those of the ALS and PD patients.

C) To ascertain the effects of immobilization due to paralysis on bone density.

LMG-IRP-NIA

LN-IRP-NIA

LCS-IRP-NIA





LMG-IRP-NIA

LN-IRP-NIA

LCS-IRP-NIA



ANNUAL REPORT OF THE LABORATORY OF CARDIOVASCULAR SCIENCE  
NATIONAL INSTITUTE ON AGING

The overall goals of the Laboratory of Cardiovascular Science are (1) to identify age-related changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to study myocardial structure and function, and response to pharmacological therapeutics in disease models, and to determine how age interacts with these chronically altered cardiac states to determine the level of myocardial function; (3) to study basic mechanisms in excitation-contraction coupling and of energy-yielding oxidative pathways in cardiac muscle; and (4) to determine the chemical nature and sequence of intermediate reactions controlling the movement of ions through ionic channels and pumps present in myocardium, specifically with respect to how the affinity, capacity and selectivity of ion translocation through membranes are affected by aging and disease. In meeting these objectives, studies are performed in human volunteers, intact animals, and isolated heart and vascular tissues, isolated cardiac cells, and subcellular organelles. Our studies during FY90 are summarized below.

Studies in Man

Age-Associated Changes in Cardiac Rhythm and Conduction. A. To determine the site of the PR interval prolongation associated with aging, we performed signal averaged high resolution surface ECGs in 161 clinically healthy Baltimore Longitudinal Study of Aging (BLSA) volunteers with normal atrioventricular (AV) conduction. An increase in PR interval with age was found in both sexes and was localized proximal to the His bundle depolarization but distal to the P wave inscription, suggesting block within the AV junction; a qualitatively similar but more pronounced delay was noted proximal to the His bundle in 7 older men with first degree AV block.

B. We have determined the prevalence and significance of exercise-induced frequent or repetitive ventricular ectopic beats (VEB) in apparently healthy BLSA volunteers. Between 1974 and 1984, 80 of 1160 such asymptomatic subjects developed frequent VEB ( $> 10\%$ ) or salvos ( $> 3$  in a row) on at least one maximal treadmill exercise test. These 80 subjects were significantly older than the larger group without such exercise-induced VEB ( $63.8 \pm 12.5$  vs  $50.0 \pm 16.1$ ,  $p < .0001$ ). Only 9 of 80 (11%) demonstrated an ischemic ST segment response to exercise. Over a mean follow-up of 4.6 years; only 8 cardiac events have occurred versus 10 events in 80 age- and sex-matched control subjects without such complex exercise-induced VEB ( $p = \text{NS}$ ).

C. The prognostic significance of 24-hr ambulatory ECG recordings was assessed in 100 healthy BLSA volunteers  $> 60$  years old. Over a mean followup of 10 years, coronary events (CE) developed in 10 subjects. The prevalence and complexity of both supraventricular (SV) and ventricular (V) ectopic beats were similar in the groups with and without CE. However, CE occurred in 2 of 5 subjects (40%) with flat or downsloping ST segment depression  $> 1.0$  mm versus only 8 of 95 (8%) without such ST changes.



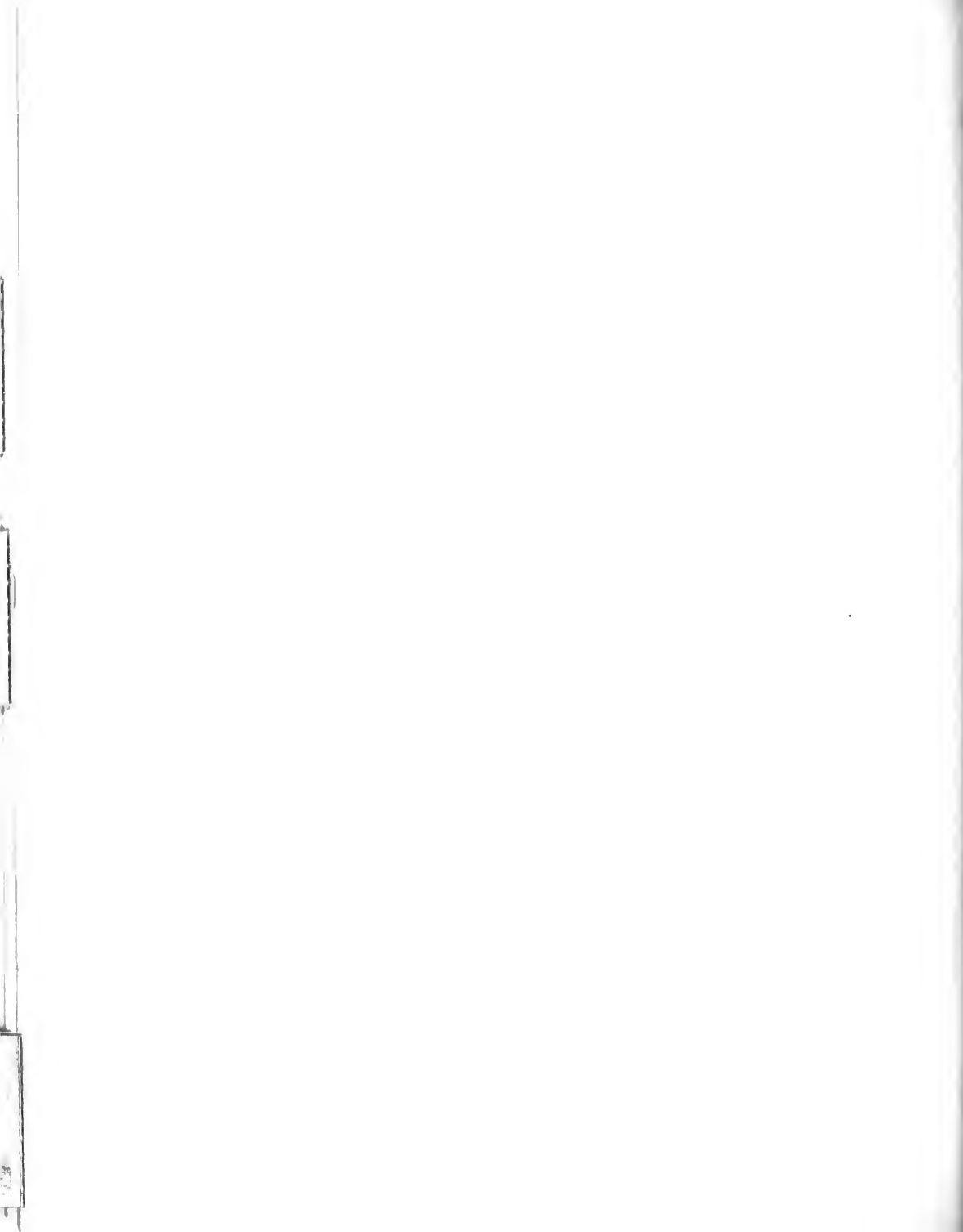
Age Associated Changes in Ventricular-Vascular Coupling. The heart and vasculature of normotensive elderly subjects may demonstrate changes of a muted form of hypertension. Left ventricular hypertrophy, a reduction in early diastolic filling, and increased vascular stiffness are features shared by the cardiovascular systems of normotensive elderly and younger hypertensive individuals. This study of ventricular-vascular coupling attempts to determine and correlate age associated changes in left ventricular mass and vascular stiffness. To date arterial pressure wave recordings have been non-invasively obtained from the carotid artery in 142 healthy normotensive BLSA participants and members of the Master Athlete study by means of a transcutaneous tonometer containing a high fidelity Millar micromanometer; pulse wave velocity measurements have been made by simultaneously obtained doppler flow recordings. Carotid pressure wave forms from the first 41 participants have been analyzed to measure the time from the shoulder to peak amplitude (PiP) and the augmentation index (AGI%). The shoulder was determined from the third derivative of the pressure tracing. A late systolic pressure peak and an increase in the pulse wave velocity were noted with advancing age. Both PIP and AGI% correlate significantly with age. Additionally LV mass determination has been made by either M-mode or 2-D echocardiography or magnetic resonance imaging. Determination of mass is pending refinements in the computer software system used for data analysis. Subsequent correlations of LV mass with PIP, AGI%, and PWV are awaiting these modifications. The reliability of tonometric measurements will be established by direct comparison of non-invasive carotid waveforms to invasively obtained aortic pressure contours. Future studies include the use of applanation tonometry to evaluate exercise induced alterations in arterial contour in various age groups.

Contract: Johns Hopkins University (N01-AG-4-2109)

Title: Non-Invasive Assessment of Cardiac Structure and Function in Aging Men and Women

During the past 12-1/2 years, rest and exercise thallium and gated blood pool cardiac scans have been performed respectively on over 750 and 300 participants in the BLSA. These studies have provided unique insights concerning the prevalence and prognostic significance of exercise-induced myocardial blood flow abnormalities (i.e. ischemia) as well as the effect of age, gender, life-style and disease on cardiac structure and function at rest during aerobic exercise. The present contract is in the second year of a 9 year renewal, during which cardiac blood pool and thallium scans are being continued in the following groups of individuals.

Although the nuclear cardiac studies are performed at Johns Hopkins Hospital, conceptualization of the specific research questions, the selection of study subjects, and the data analyses are the responsibility of the LCS. Dr. Jerome Fleg and Dr. Edward Lakatta direct the overall research effort and review the collected data and plan data analyses with statisticians from our laboratory. The exercise studies are performed under the supervision of Dr. Gary Gerstenblith and the scans are read by Dr. Lewis Becker, both from the Johns Hopkins Cardiology Division. This long-standing collaboration continues to bear fruit as evidenced by a substantial number of publications in top quality peer-reviewed research journals.



LMC-IRP-NIA  
IN-IRP-NIA

**A. Rest and Exercise Gated Cardiac Blood Pool Scans**

1. Longitudinal Study of Cardiac Function. In 100 men and women who have had blood pool scans at least 5 years previously, the test will be repeated, with simultaneous measurement of oxygen consumption ( $\text{VO}_2$ ). This will allow insight into longitudinal changes in cardiac function at rest and during exercise. The  $\text{VO}_2$  data will provide information regarding central (cardiac) versus peripheral (arteriovenous oxygen difference) mechanisms for maintaining  $\text{VO}_2$  with advancing age.

2. Cardiac Function in Highly Trained Seniors, Sedentary Subjects Pre- and Post-Training, and Obese Individuals Pre- and Post-Weight Loss. These scans, all performed with simultaneous  $\text{VO}_2$  measurements, will allow determination of the central and peripheral effects of conditioning status and obesity on aerobic exercise performance, and the interrelations of such lifestyle variables with the aging process.

3. Cardiac Function in Patients with Latent Coronary Artery Disease (CAD). Preliminary data from such individuals with abnormal exercise ECG's and/or exercise thallium scans, suggest that ischemia and advanced age have additive effects on certain cardiac parameters. Extension of these studies will allow more accurate characterization of this interaction between age and latent CAD and help to clarify discrepancies in the cardiovascular aging literature which have resulted from the inclusion of such individuals with latent CAD in some studies but not others.

4. Cardiac Function in Patients after Cardiac Transplantation. Stable outpatients who are at least six months past cardiac transplantation will undergo rest and exercise scans with simultaneous measurement of  $\text{VO}_2$ . By comparing the responses of these patients with age- and gender-matched BLSA normals, we will gain insights regarding the effect of cardiac denervation on the cardiovascular response to exercise.

5. Additional Studies in Normals with simultaneous measurement of  $\text{VO}_2$ . In other BLSA volunteers who have no evidence of CAD by all available criteria, these scans should be made:

a. To contrast the effect of age in men with its effect in women on the cardiovascular response to stress.

b. To evaluate the effect of age on the response to other commonly employed drugs used to treat large numbers of elderly individuals, e.g., vasodilators.

c. To provide a base of 350-400 individuals for a longitudinal evaluation of the effect of age itself on cardiovascular function.

**B. Thallium Perfusion Scans**

Participants in the Baltimore Longitudinal Study of Aging would continue to undergo exercise thallium tests as they become eligible to do so in the next 4 years. This would include those who become 40 years of age, those who enter the program, and those who are capable of undergoing a treadmill test but who for one reason or another did not have a

2





thallium test during the past 5 years. This would enable us to continue to identify asymptomatic reversible ischemia in the BLSA participants and allow us to better assess the accuracy of a positive test in asymptomatic individuals in predicting the future development of clinical ischemic events. In addition, repeat thallium scans will be initiated on subjects who last underwent such scans at least 10 years previously. These repeat scans will allow assessment of the longitudinal development and progression of both latent and overt CAD, identification of risk factors associated with disease progression and determination of the prognostic significance of longitudinal changes in these perfusion scans.

**Effects of Age and Gender on Exercise Cardiac Performance.** A. To determine the independent effects of age and gender on the left ventricular ejection fraction (LVEF) response to upright cycle exercise, we performed gated blood pool scans at rest and maximal upright cycle exercise in 93 men and 49 women ages 23-86 yrs free of heart disease by history, physical exam, rest and exercise ECG and if >40 yr old, exercise thallium scan. The change in LVEF ( $\Delta$ LVEF) from rest to maximal workload (MWL) declined in men from  $22 \pm 6$  units under the age of 40 yrs to  $10 \pm 9$  units if older than 60; corresponding values in women were  $17 \pm 6$  below age 40 and  $3 \pm 10$  above age 60 yrs. The specificity of a  $\Delta$ LVEF  $\geq 5$  units for the absence of coronary artery disease (CAD) was 100% for all subjects younger than 40 yrs but decreased to 70% and 54% respectively in men and women aged 60 and beyond. By multiple regression analysis both age ( $p < .0001$ ) and gender ( $p < .05$ ) were independent determinants of  $\Delta$ LVEF ( $\Delta$ LVEF =  $32.2 - 0.26 \text{ age} - 4.4 \text{ sex}$ ) but only age ( $p < .0006$ ) predicted absolute LVEF at MWL. Thus, both increasing age and female sex independently diminish  $\Delta$ LVEF in healthy subjects, decreasing the specificity of  $\Delta$ LVEF for CAD.

B. To examine gender differences in exercise hemodynamics in older subjects, we performed gated blood pool cardiac scans at rest and during maximal upright cycle exercise in 45 healthy volunteers  $\geq 60$  years old with normal resting and treadmill ECG and thallium scans. At rest, end-diastolic and end-systolic volume indices (EDVI and ESVI) were larger in men than women ( $77.4 \pm 3.2$  vs  $64.4 \pm 3.3$  ml/M<sup>2</sup>,  $p < .02$  and  $27.7 \pm 1.7$  vs  $19.9 \pm 1.6$  ml/M<sup>2</sup>,  $p < .01$ ) respectively. Resting stroke volume index (SVI), cardiac index (CI), and heart rate (HR) were similar. At maximal workload (MWL) which was  $122 \pm 4.2$  watts in men vs  $79 \pm 5.1$  in women,  $p < .01$ , EDVI ( $87 \pm 3.5$  vs  $74 \pm 4.6$  ml,  $p < .05$ ), SVI ( $63 \pm 2.3$  vs  $53.7 \pm 2.6$  ml,  $p < .01$ ) and CI ( $8.5 \pm 0.3$  vs  $7.4 \pm 0.4$  l/min/M<sup>2</sup>,  $p = .06$ ) were larger in men whereas HR was higher in women ( $147 \pm 4.5$  vs  $137 \pm 2.9$  beats/min,  $p = .06$ ). When older men and women matched for fitness level (MWL of 75-100 watts) were compared, all hemodynamics were similar at rest and at MWL except for the higher HR at MWL in women,  $149 \pm 5.0$  vs  $129 \pm 3.8$  beats/min,  $p < .01$ . Thus, smaller resting and exercise ventricular volumes in older women are mediated by their lower fitness level.

**Regulation of Left Ventricular Volumes in Normal Man.** A. To determine the extent to which L. ventricular end-systolic volume (ESV) "follows" the end-diastolic volume (EDV) response to various perturbations, we measured EDV and ESV by gated blood pool scan in 119 healthy, rigorously screened BLSA volunteers ages 21-81 yr in response to postural shift, during graded upright cycle exercise in an additional 31 subjects who exercised during  $\beta$ -adrenergic blockade (propranolol 0.15 mg/kg) and in 18 older men during lower body negative pressure. Multiple regression analysis showed that the changes in ESV ( $\Delta$ ESV)



during a postural shift or during graded exercise was highly statistically correlated with the change in EDV ( $\Delta$ EDV) that occurred ( $r^2$  ranged from 0.34 to 0.49, correlation is positive) regardless of age, sex, or exercise workload. Thus, diverse perturbations of left ventricular EDV caused by postural stress, cycle exercise and  $\beta$ -adrenergic blockade result in parallel changes in ESV.

B. The increasingly sedentary lifestyle associated with aging may account for some age-related alterations in cardiac function. We tested whether vigorous endurance training (ETR) in older men prevented the normal age-related decrease in peak filling rate (PFR) in EDV/sec and increased time to PFR, (TPFR) in msec, by comparing rest and exercise gated blood pool scans (20 frames/RR) from 12 ETR senior master athletes (O-ETR) (mean age=65.4,  $\text{VO}_2$  max (ml/kg/min)=51.5), 12 sedentary older men (O-C) (age=66.8),  $\text{VO}_2$  max=32.3) and 8 young men (Y)(age=33.1). Both O-ETR and O-C had negative exercise thallium scans. Data =  $\pm$  S.D.

	Rest	50 Watt	100 Watt
PFR,O-ETR	2.11 $\pm$ .38	3.74 $\pm$ .58	4.57 $\pm$ 1.06
PFR,O-C	2.13 $\pm$ .53	4.16 $\pm$ .73	5.53 $\pm$ 1.73
PFR,Y	3.91 $\pm$ .91*	5.69 $\pm$ .83*	6.82 $\pm$ 1.64*

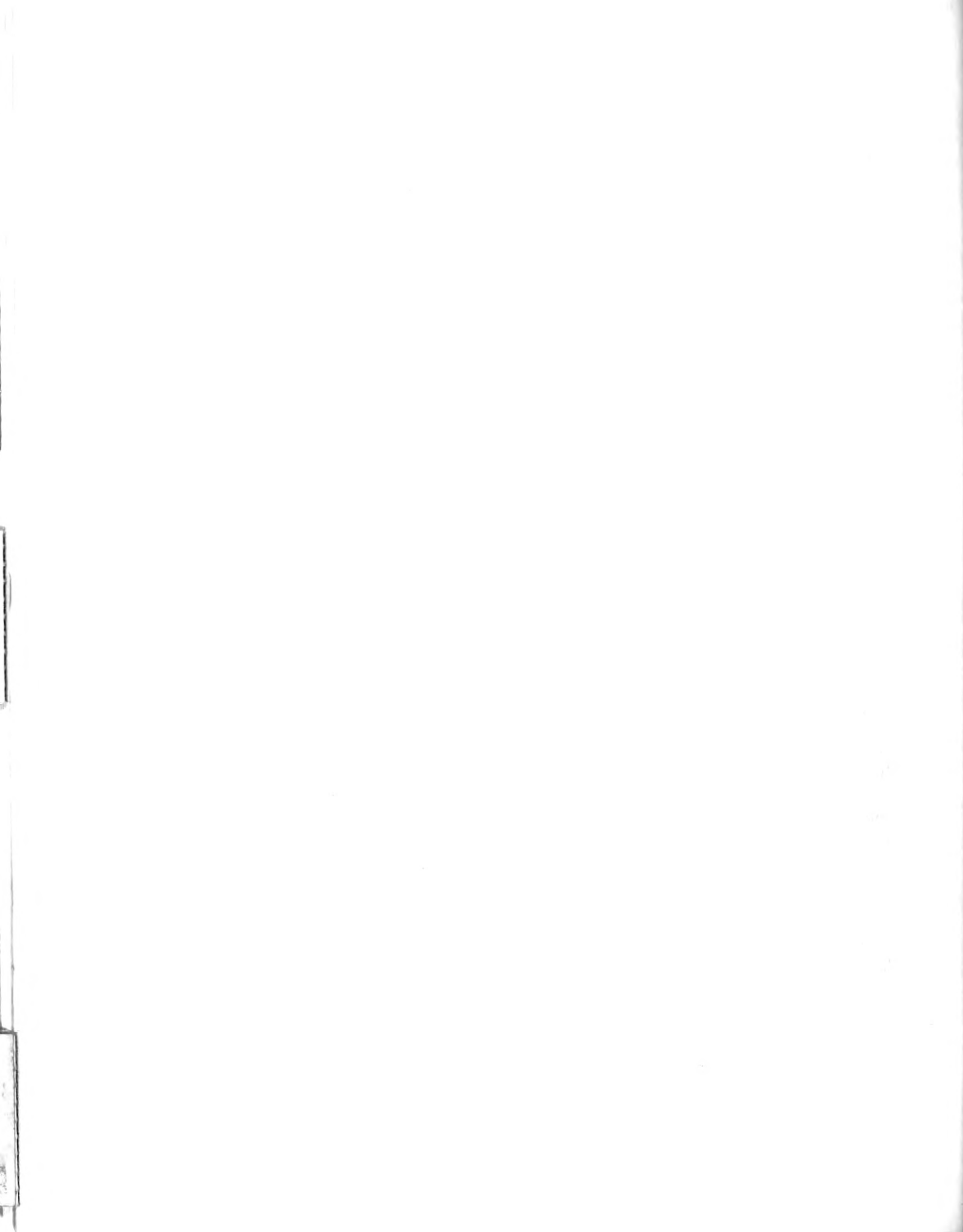
\*p < 0.01 vs O-ETR and O-C; +p < 0.01 vs O-ETR.

Heart rate adjusted PFR, as well as TPFR also did not differ between O-Ex and O-C. Thus, ETR does not prevent the altered diastolic filling characteristics associated with normal aging.

### Studies in Animal Models

Progressive Changes in mRNA of Rat Cardiac Myosin Heavy Chain Genes With Adult Aging. Cardiac cell enlargement occurs in response to chronic arterial pressure overload in young rodents and with advanced adult age in normotensive rodents. Cardiac muscle of both senescent and pressure overloaded hearts exhibit a nearly identical pattern of altered cardiac excitation-contraction mechanisms, among which are a reduced contraction velocity, a reduction in the myosin ATPase activity, a marked increase in the expression of the  $V_3$  ( $\beta$  myosin heavy chain, MHC) and a reduction in  $V_1$  ( $\alpha$  MHC) isoforms. In the heart of younger hypertensive adult rodents, this shift in MHC isoforms is due, in part at least, to changes in transcription rates of  $\beta$  and  $\alpha$  MHC genes. The present study was undertaken to determine whether the marked shift MHC proteins occurring with age between adulthood and senescence is also associated with changes in MHC gene expression. Levels of mRNA coding for  $\alpha$  and  $\beta$  MHC were determined by Northern analysis and dot blots (oligonucleotide probes on pooled RNA purified from 6 hearts each of animals of a broad age range. The mRNA for  $\beta$  MHC increased greater than fourfold from 1 to 24 months and the mRNA for  $\alpha$  MHC decreased by a proportional amount. Thus, the phenotypic, biophysical and biochemical cardiac contractile changes with adult aging are, in part at least, due to changes in gene expression.

Novel Single Cell Techniques in the Study of Myocardial Contractility, Adaptation, and Aging. Novel single cell techniques have been developed which permit the simple and reproducible characterization of the length/load-dependent contractile performance of single adult mammalian heart cells, with the simultaneous measurement of the transient change in cytosolic calcium, as indexed by changes in indo-1 fluorescence. Cells are embedded in



a transparent, elastic polymer matrix which enables reversible gradations (via matrix stretch) in resting and stimulated-auxotonic-contraction length. Length-dependent  $\text{Ca}^{2+}$  myofilament activation and load dependent relaxation have been demonstrated for the first time in single mammalian ventricular myocytes with this technique. The utility of various indices derived from edge motion measurements, including edge acceleration and relative impulse of the force, have been applied to this technique for the first time and have been demonstrated as valid indices of "contractility," in lieu of actual measured force. Techniques have also been developed which permit the non-destructive, selective loading of calcium fluorescent indicators (such as indo-1 "free acid") into the myoplasm of large numbers of heart cells, overcoming past limitations of nonselective organelle dye-loading (especially mitochondria) complicating the use of membrane-permeant dye-ester derivatives and preventing rigorously-valid  $\text{Ca}^{2+}$  calibration. Work is proceeding along these lines to perfect a routine, practical method to obtain validly calibrated myoplasmic  $\text{Ca}^{2+}$  transients for these contractility studies. Viable human heart cells from atrial and ventricular chunk surgical specimens are successfully isolated via enzymatic techniques in our lab on a regular basis, and will be studied by these techniques. A growing body of evidence supports the concept that cardiac adaption to hemodynamic stress is reduced with aging, playing a significant role in the pathogenesis of human disease. However, the underlying molecular mechanisms and factors regulating cardiac growth and resulting myocardial function are incompletely understood. Techniques are thus being developed in this isolated single heart cell model to correlate graded cell stretch and loading,  $\text{Ca}^{2+}$  and age, with contractile function, the expression of proto-oncogene and heat shock protein mRNA, and changes in contractile protein gene isoform expression (i.e. coding for  $\alpha$  skeletal actin,  $\beta$  myosin heavy chain), via in situ hybridization.

Excitation-Contraction Mechanisms in Isolated Cardiac Cells. Two general modes of amplitude modulation of the cardiac contraction are a variation (a) in the number of  $\text{Ca}^{2+}$  ions made available to bind to the myofilaments during the transient increase in cytosolic calcium concentration ( $\text{Ca}_i$ ) following excitation and (b) in the extent of myofilament displacement or force production in response to a given  $\text{Ca}_i$  transient. In order to determine the extent to which a change in the twitch contraction amplitude in intact cardiac cells or muscle is due to either mechanism contraction needs to be assessed simultaneously with measurements of the  $\text{Ca}_i$  transient. A direct assessment of the relationship between  $\text{Ca}_i$  and cell length, and thus myofilament length, can be made in the absence of external mechanical loading in individual isolated cardiac cells. We have designed a method to simultaneously measure contraction and  $\text{Ca}_i$ , as reported by the fluorescent  $\text{Ca}^{2+}$  probe, indo-1 in individual cardiac cells to examine the relationship between  $\text{Ca}^{2+}$  and contraction. During relaxation of the twitch contraction originating from slack length under a given set of conditions, a unique relation exists between cell length and  $\text{Ca}_i$  during twitches that vary in their individual amplitudes manifest as a single trajectory in the cell length- $\text{Ca}_i$  or indo-fluorescence phase plane diagrams. This  $\text{Ca}_i$ -length relationship during electrically stimulated twitches is steeper than that described by peak contraction amplitude versus peak  $\text{Ca}_i$  relationship and is identical to that due to increases in  $\text{Ca}_i$  and contractions elicited via the abrupt and transient application of caffeine or by "tetanization" of the cell in the presence of ryanodine. This unique relationship between  $\text{Ca}^{2+}$ -dependent fluorescence and length shifts appropriately in response to perturbations that have previously demonstrated to alter the steady-state myofilament  $\text{Ca}^{2+}$  sensitivity in skinned cardiac fibers. Thus, the  $\text{Ca}_i$  cell length trajectory during the relaxation phase of contraction appears to define a

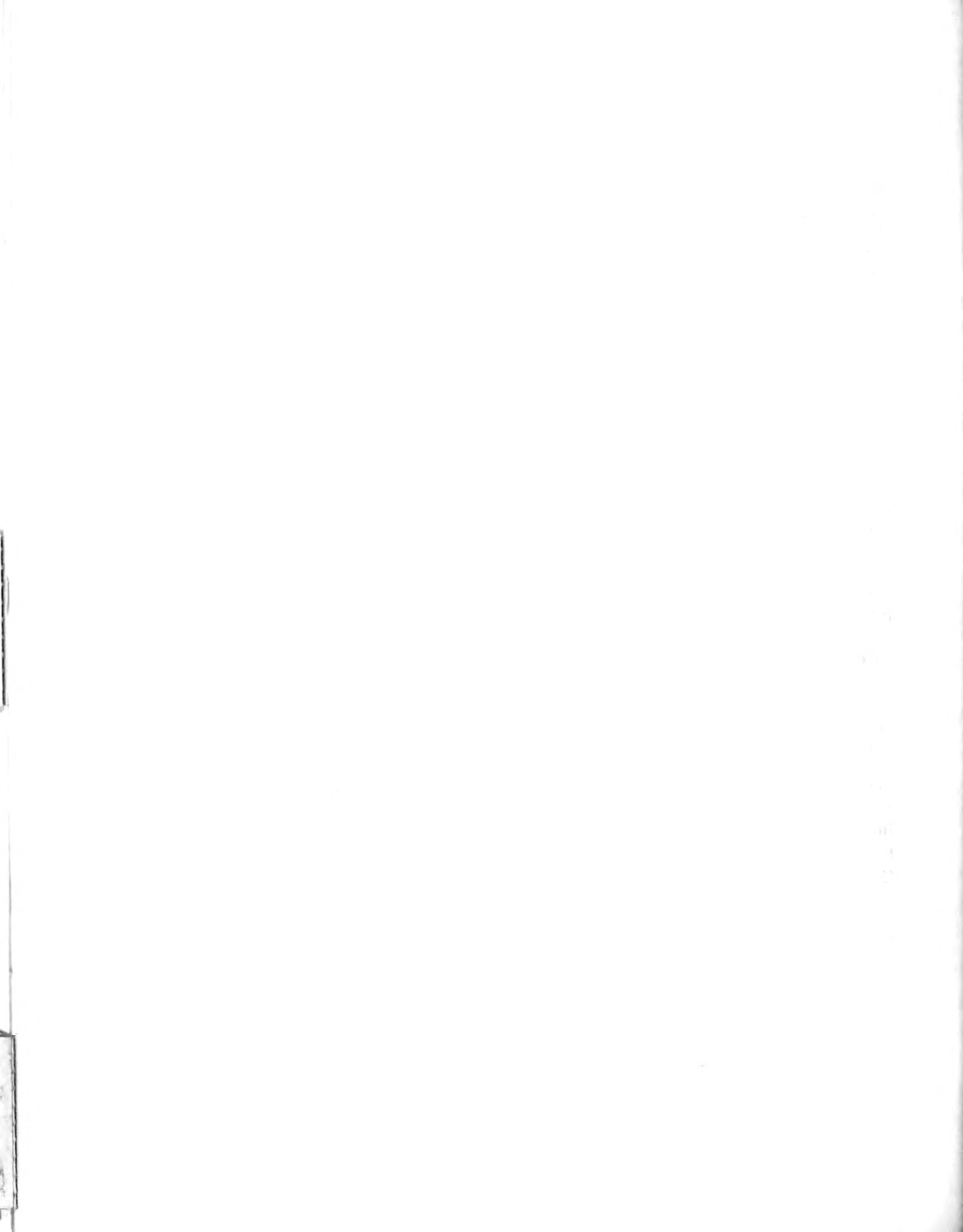


quasi-equilibrium of cytosolic  $[Ca^{2+}]$  and myofilament  $Ca^{2+}$  binding and may be used to assess the myofilament  $Ca^{2+}$  response during the twitch contraction in single cardiac myocytes.

**Cytosolic Calcium Modulation of the Action Potential.** The role of the cytosolic  $Ca$  ( $Ca_i$ ) transient in determining the configuration of the cardiac action potential was investigated. For this purpose, rat ventricular myocytes loaded with the  $Ca^{2+}$ -sensitive fluorescent dye indo-1 were used. Myocytes were loaded with either 1) the acetoxy-methyl ester of indo-1 (indo-1 AM), which provides qualitative information about changes in the  $Ca_i$  transient or 2) the  $Ca^{2+}$ -sensitive, free acid form of indo-1, which allows intracellular  $Ca_i$  to be quantified. The magnitude of the  $Ca_i$  transient was graded by various physiological and pharmacological interventions and membrane voltage or current was recorded using patch-type microelectrodes. Earlier work in indo-1 AM loaded cells had shown that phase-plane loops of membrane potential ( $V_m$ ) vs indo-1 ratio from a stimulus train conformed to a common trajectory during the slow tail of repolarization, despite a beat-dependent decrease in the magnitude of the  $Ca_i$  transient. It was found that phase-plane loops of the  $V_m$  vs. indo-1 ratio from spontaneous diastolic  $Ca_i$  oscillations also conformed to this trajectory. Experiments with indo-1 free acid, which was incorporated into the cell by inclusion in the microelectrode filling solution, showed that in rested beats peak  $Ca_i$  can exceed  $2 \mu M$  and then decrease to  $0.4 - 0.6 \mu M$  in the steady state. Evidence was found that both electrogenic  $Na/Ca$  exchange and a  $Ca^{2+}$ -dependent ion channel current may participate in the modulation of the cardiac action potential by the  $Ca_i$  transient.

**pH Regulation in Cardiac Myocytes.** Physiological studies have been aided by the use of intracellular indicators. Indicators for intracellular calcium and pH are used in monitoring physiological and pathophysiological properties of isolated cardiac myocytes and intact cardiac tissue. This project developed a novel time resolved system for cytosolic pH measurements using the recently synthesized intracellular pH indicator, SNARF-1, seminaphthorhodalfleur, with simultaneous measurements of cell length. The emission spectrum of SNARF-1 contains two well separated emission peaks at 590 and 640 nm. This feature allows the indicator to be used in the single excitation, dual emission, ratio mode; analogous to the calcium indicator, INDO-1. SNARF-1 is available in both the free acid form and as a cell permeant acetoxymethyl ester. We have found that isolated cardiac myocytes are easily loaded with ester, and have the following characteristics: 1) a consistent intracellular calibration can be obtained, 2) the contractile properties are essentially unchanged in the presence of the indicator, 3) the indicator is present primarily in the cytosol (95% to 100%) with virtually no partitioning into the mitochondria, 4) the indicator is retained for several hours at room temperature, and 5) steady-state pH and transient changes in pH are easily monitored. Changes in pH can be monitored during important physiological and pathophysiological perturbations. The initial applications of the SNARF-1 system include 1) pH regulation and changes in contractile state during anoxia, acidosis, and anesthesia and 2) receptor mediated changes in contractile state.

**Effects of  $\beta$ - and  $\alpha$ -Adrenergic Stimulation on Cytosolic pH in Cardiac Myocytes.** Both  $\beta$ - and  $\alpha$ -adrenergic receptor agonists have a positive inotropic effect on the heart. Their action is associated with an increase in the cytosolic  $[Ca^{++}]$  ( $Ca_i$ ) transient and also with a change in myofilament responsiveness to  $Ca^{++}$ .  $\alpha$ -Adrenergic agonists appear to enhance myofilament responsiveness to  $Ca^{++}$  and this effect may contribute to the increase in contractility. In contrast  $\beta$ -adrenergic stimulation of the heart decreases myofilament  $Ca^{++}$





sensitivity and it has been suggested that this effect may contribute to the "relaxing" action of  $\beta$ -adrenergic stimulation. In non-myocardial cells  $\alpha$ -adrenergic stimulation has been shown to increase cytosolic pH ( $\text{pH}_i$ ), probably via an increase in phosphatidylinositol turnover leading to protein kinase C mediated activation of  $\text{Na}^+/\text{H}^+$  exchange. Interventions that increase cAMP can also modulate  $\text{Na}^+/\text{H}^+$  exchange and either decrease  $\text{pH}_i$  (e.g. epithelial cells) or increase  $\text{pH}_i$  (e.g. red blood cells). In the myocardium, myofilament sensitivity to  $\text{Ca}^{2+}$  is profoundly affected by changes in  $\text{pH}_i$  and the contractility of the heart is decreased by acidosis and increased by alkalosis. Thus, we investigated the effect of  $\beta$ - and  $\alpha$ -adrenergic stimulation on  $\text{pH}_i$  in myocardial cells from the adult rat, loaded with the  $\text{pH}_i$  probe SNARF-1. Cells in bicarbonate buffer were studied during electrical stimulation and at rest. Isoproterenol increased twitch amplitude and had no effect on  $\text{pH}_i$ . In contrast,  $\alpha$ -adrenergic stimulation with phenylephrine and nadolol enhanced twitch amplitude and increased  $\text{pH}_i$ . There was a significant correlation between the increase in twitch amplitude and  $\text{pH}_i$ . Both effects were antagonized by ethylisopropylamiloride a  $\text{Na}^+/\text{H}^+$  inhibitor. Thus  $\alpha$ -adrenergic stimulation which stimulates phosphatidylinositol turnover increases  $\text{pH}_i$  and this may contribute to its positive inotropic action. In contrast,  $\beta$ -adrenergic stimulation, which increases cAMP has no effect on  $\text{pH}_i$  in myocardial cells.

**Opioids Increase  $\text{IP}_3$  and Cytosolic  $\text{Ca}^{2+}$  in Cardiac Myocytes and Neurons.** Opioid peptides modulate neurotransmitter release and myocardial contraction. However, the cellular mechanisms underlying their effects are not known. In particular, their effects on cytosolic  $\text{Ca}^{2+}$  ( $\text{Ca}_i$ ) homeostasis are still largely undefined. The present study shows that in rat ventricular myocytes loaded with the  $\text{Ca}^{2+}$  probe indo-1, the  $\kappa$  opioid receptor agonist (trans-(dl)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclo-hexyl]-benzenacetamide) methane sulfonate hydrate (U-50,488H) causes a transient increase followed by a monotonic decrease in the amplitude of the twitch and of the  $\text{Ca}_i$  transient, indexed as the 410/490 nm ratio of indo-1 fluorescence. Under similar conditions the  $\delta$  opioid leucine-enkephalin decreases twitch and  $\text{Ca}_i$  amplitudes without causing a transient increase in either signal. In the absence of electrical stimulation U-50,488H and leucine-enkephalin slowly increase  $\text{Ca}_i$  or cause  $\text{Ca}_i$  oscillations and eventually abolish the caffeine-triggered  $\text{Ca}_i$  transient. This occurs in both myocytes and neuroblastoma-2a cells. These effects of the U-50,488H and leucine enkephalin on both cell types are prevented by the  $\kappa$  and  $\delta$  opioid receptor blockers (-)-N-(3-Furylmethyl)- $\alpha$ -normetazocine methansulphonate (Mr 1452) and naloxone. In cardiac myocyte suspensions U-50,488H and leucine-enkephalin both cause a rapid and sustained increase in inositol-1,4,5-trisphosphate ( $\text{IP}_3$ ). The peak effect of the  $\kappa$  agonist on  $\text{IP}_3$  production is of greater magnitude and occurs with a faster time course than that of the  $\delta$  opioid and may account for the different effects of these peptides on the  $\text{Ca}_i$  transient in electrically stimulated cardiac myocytes. Thus, both in cardiac cells and neurons  $\kappa$  and  $\delta$  opioid receptors appear to be coupled to phosphatidylinositol turnover leading to  $\text{Ca}^{2+}$  release from intracellular stores.

**Novel Positive Cardiac Inotropic Agents.** All positive inotropic agents that are available for clinical use exercise their effect predominately via an increase in cell calcium loading. However once the myocardial preparation has reached its peak contractile response a further increase in cell calcium loading is associated initially with a plateau and then with a decline in the inotropic state of the muscle, an increase in diastolic tone, aftercontractions and arrhythmias. This condition which has been defined as "calcium overload" represents the limiting factor in the clinical use of positive inotropic agents. Thus, it is desirable to



develop drugs that increase the contractility of the heart via an enhancement in myofilament responsiveness to calcium rather than by increasing the extent of cell calcium loading. We tested the effect of novel thiadiazinone derivatives (designed by E. Merck, Darmstadt, FRG) that vary in potency (1) to sensitize skinned myocardial fibers to  $\text{Ca}^{2+}$ : EMD 54622  $\geq$  53998 > 54650, and (2) to inhibit phosphodiesterase III in cell homogenates (54650  $\geq$  53998 > 54622). We determined whether differential  $\text{Ca}^{2+}$ -myofilament effects are expressed in intact guinea pig cells, bathed in Hepes buffer (23°C) and loaded with the fluorescent  $\text{Ca}^{2+}$  probe, indo-1. Our results show that the steepness of relationship among twitches and indo-1 fluorescence transients measured across drug dose varies as 54622 > 53998 > 54650. Thus, differential modifications of the myofilament  $\text{Ca}^{2+}$  response in intact cells can be effected via molecular modifications of thiadiazinone that enhance its potency to sensitize myofilaments to  $\text{Ca}^{2+}$ .

**Mechanism of Post-Hypoxic Impaired Myocyte Relaxation.** Striking changes in the time course of myocardial contraction have been documented during and following brief periods of ischemia or hypoxia. These studies have been conducted in whole tissue preparations and have allowed only partial delineation of the mechanisms underlying these changes in mechanics. Recent technical advances have allowed the more detailed study of these events at the single cell level. A special chamber, developed in our laboratory, was employed to study contraction in single cells during and after brief periods of profound hypoxia ( $\text{pO}_2 < .02$  torr). Rat ventriculocytes, loaded with the calcium-sensitive fluorescent probe indo-1, showed no early failure of contraction upon exposure to hypoxia, however marked changes in the timing of cell contraction and relaxation occurred early during hypoxia and at reoxygenation following brief hypoxia (10 minutes at 23° C). During hypoxia time to peak contraction (TPK) and time to 50% relaxation (RT50) were abbreviated without a significant change in the time to 90% relaxation (RT90). The timing of the calcium transient was unaffected. At reoxygenation TPK, RT50 and RT90 were markedly prolonged again without any change in the timing of the calcium transient. Simultaneous measurement of the action potential and contraction in current-clamped cells showed similar mechanical changes without a change in the AP. We have recently documented a transient rebound intracellular alkalosis (using the pH sensitive fluorescent probe SNARF-1) which occurs at reoxygenation and may contribute to the slowing of relaxation seen at reoxygenation by slowing myofilament relaxation kinetics.

**Mechanism of Oxidant-Induced Intracellular Calcium Loading in Cardiac Myocytes.** Cardiac myocyte injury occurring at reperfusion following a period of ischemia likely results in part from intracellular calcium loading which may be due to the effects of reactive oxygen species which are generated at reperfusion. We previously established that oxygen derived free radicals cause calcium loading and injury in isolated myocytes exposed to an exogenous hydroxyl radical generating system. The present study focuses on the mechanism of radical induced calcium loading in adult rat cardiac myocytes. During exposure to hydrogen peroxide and iron (generates reactive hydroxyl radical) single myocytes demonstrated a transient increase in twitch amplitude following electrical field stimulation and a progressive shortening of diastolic cell length consistent with intracellular calcium loading. Aftercontractions later developed and finally the cell became inexcitable and underwent contracture. Cytosolic calcium, measured with the fluorescent probe indo-1, rose following the administration of the radical generating system. The cellular action potential, monitored with whole-cell clamp techniques, demonstrated marked progressive plateau



prolongation without depolarization of the resting potential. Progressive cell shortening and twitch amplitude augmentation were prevented by stimulating the cell under voltage clamp with fixed duration depolarizations. Unstimulated cells failed to demonstrate progressive cell shortening prior to the abrupt onset of contracture. The currents underlying the prolongation of the action potential were studied. A progressive decrease in the magnitude of the calcium current was noted during radical exposure.  $I_{K1}$ , the inwardly rectifying  $K^+$  current, was inhibited and likely contributes to action potential prolongation, which ultimately leads to cellular calcium loading.

Spontaneous  $Ca^{2+}$  Release in the Intact Heart During Ischemia and Reflow. Spontaneous, asynchronous, myocardial calcium oscillations, have been attributed to calcium-dependent calcium release from the sarcoplasmic reticulum (SR) and exhibit a periodicity which depends upon the extent of cell calcium loading. In thin excised cardiac muscle the inhomogeneous contractile motion caused by the spontaneous oscillations phase modulates a laser beam, producing intensity fluctuations in the scattered light (SLIF). In the present project we measured intensity fluctuations of 633 nm laser light backscattered from the epicardial surface of isolated, perfused rat and rabbit hearts. The frequency of SLIF was increased by maneuvers that raise intracellular calcium. SLIF were abolished by removal of extracellular calcium with ethylene glycol-bis ( $\beta$ -aminoethyl ether)-N,N,N',N'-tetraacetic acid and by blockade of SR calcium release by ryanodine. SLIF were not accompanied by any surface electrocardiogram and were not abolished by 144 mM extracellular potassium. SLIF were absent in rabbit hearts under base-line conditions but could be provoked by calcium loading using zero potassium and ouabain. Thus, SLIF monitors the microscopic motion caused by intracellular calcium oscillations in the intact heart.

Delayed recovery of contractile function after myocardial ischemia may be due to increased calcium loading. To examine this potential mechanism, SLIF were studied in isolated atrioventricularly blocked rat hearts during and after 60 min of ischemia at 30°C. After reperfusion developed pressure evidenced a small recovery but then fell abruptly. This was accompanied by an increase in end-diastolic pressure to  $37 \pm 5$  mm Hg and a fourfold increase in SLIF, to  $252 \pm 58\%$  of baseline. In another series of hearts initial reperfusion with calcium of 0.08 mM prevented the SLIF rise and resulted in improved developed pressure ( $74 \pm 3\%$  of control), and lower cell calcium ( $5.9 \pm 3$  vs  $10.3 \pm 1.4$   $\mu\text{mol/g}$  dry wt). Thus, during reperfusion delayed contractile recovery can be attributed, in part, to an adverse effect of calcium loading which can be indexed by increased SLIF occurring at that time.

Regulation of Energy Metabolism. This project is designed to explore the regulation of energy provision by the process of oxidative phosphorylation and the changes which occur as a function of senescence and of disease-states. Particular emphasis is placed upon the control of substrate oxidation at the level of mitochondrial dehydrogenase enzymes. We have shown previously that the increased availability of the  $Ca^{2+}$  ion to the mitochondria during the performance of active muscular work allows the activation of three dehydrogenases, viz, pyruvate, isocitrate and 2-oxoglutarate dehydrogenase, which catalyze non-equilibrium steps in the terminal pathway of substrate oxidation. This allows the more rapid generation of NADH, the substrate for oxidative phosphorylation, and minimizes the degree to which the tissue adenine nucleotide phosphorylation potential falls during



increased muscle work. This year we have investigated the control of intramitochondrial free  $Mg^{2+}$  concentration ( $[Mg^{2+}]_m$ ), as this is a potential regulator of the interconversion of pyruvate dehydrogenase between active (dephospho) and inactive forms. Furthermore,  $[Mg^{2+}]_m$  affects the sensitivity to  $[Ca^{2+}]_m$  of all three dehydrogenase enzymes mentioned above, with less  $Ca^{2+}$  required for activation as  $[Mg^{2+}]_m$  increases. The availability of a fluorescent  $Mg^{2+}$ -chelator, Mag-fura, has made  $[Mg^{2+}]_m$  accessible to investigation for the first time. Results indicate that  $[Mg^{2+}]_m$  is maintained near to values of cytosol free  $Mg^{2+}$ , despite the large electrical potential, negative inside, across the mitochondrial membrane. Further, all procedures which raise mitochondrial free  $Ca^{2+}$  ( $[Ca^{2+}]_m$ ) above approximately  $0.5\mu M$  result in an increase in  $[Mg^{2+}]_m$ : this may form part of the mechanism whereby net transport of  $Ca^{2+}$  into the mitochondria raises the content of active pyruvate dehydrogenase, as we have shown previously. Addition of ATP and ADP in physiological concentrations to respiring, coupled mitochondria also resulted in an increase in  $[Mg^{2+}]_m$ : this was linked to a rise in  $[Ca^{2+}]_m$  and is a result which warrants further study. This year we have also begun to examine more quantitatively the linkage of dehydrogenase activation to oxidative phosphorylation by measuring the mitochondrial proton electrochemical gradient as a function of  $Ca^{2+}$ -ion availability, during the oxidation of non-saturating, physiological concentrations of 2-oxoglutarate. The membrane potential is quantitated by fluorescence of rhodamine 1,2,3, a potential-sensitive probe, and the transmembrane pH gradient by fluorescence of BCECF, a relative of fluorescein. Experiments indicate that both components of the overall proton electrochemical gradient, which is the intermediate between oxidations and phosphorylation, decrease to a smaller extent upon initiation of ADP phosphorylation if  $Ca^{2+}$  is present to activate the dehydrogenase.

As part of our study of bioenergetics and aging we have examined the activity of the mitochondrial isozyme of creatine kinase in preparations from young adult and senescent rats. This enzyme catalyses the preferred phosphorylation of cytosolic creatine by ATP exported from the mitochondrial matrix and has been shown to be less active in hypertrophy. Spectrophotometric assays of activity show no statistically significant changes in activity from 6 to 24 months of age. Nor does the fractional stimulation by creatine of State 4 (resting) respiration of mitochondria, a test which obviates potential problems due to differential purity of the different mitochondrial preparations. However, there is a tendency towards lowered activity in both types of assay and more work is required.

In the area of the energetics of heart failure, we have this year begun a study of mitochondrial functioning in the heart of the cardiomyopathic Syrian hamster (both BIO 14.6 and T.O. strains). There is a clear implication of compromised delivery of pyruvate to the mitochondria or of functioning of the pyruvate dehydrogenase complex in literature results with this animal model. We have perfused hearts under standardized conditions of work performance and are currently assaying steady-state concentrations of pyruvate in the freeze-clamped hearts. Further experiments will measure  $Ca^{2+}$  content of rapidly-isolated mitochondria, in order to be able to pin-point lesions in the functioning of the pyruvate dehydrogenase, which may be linked to changes in  $Ca^{2+}$ -ion homeostasis. Finally, in a collaboration with Dr. Weiss and Dr. Gerstenblith of the Division of Cardiology, Johns Hopkins University Department of Medicine, we have been studying glycogen metabolism in ischemia and reperfusion of the heart. Glycolytic ATP production may be essential for myocyte survival following an ischemic episode. We have studied myocardial glycogen content, using  $^{13}C$ nmr, the activation status of the glycogen phosphorylase enzyme and the





tissue content of the factors which regulate phosphorylase (Pi, glucose 6-phosphate, AMP) during zero-flow and low-flow ischemia and subsequent reperfusion. Glycogen content falls during ischemia, as expected, but then continues to fall during the first few minutes of perfusion. This latter effect cannot be explained by the fractional activation of phosphorylase (ie % phosphorylase  $a$ ) but instead correlates well with the elevated concentration of the phosphorylase substrate, Pi, which we find at that time. Further studies are in progress relating to substrate-preference of the ischemic and reperfused heart, viz discrimination between carbohydrate and fatty acid for oxidation.

**Ion Transport Mechanisms and Aging.** Kinetic investigations of the electrical behavior and enzymatic partial reactions of the ATP-dependent  $\text{Na}^+, \text{K}^+$  and  $\text{Ca}^{2+}$  pumps have demonstrated that the phosphoenzyme conformational transition is an electrogenic step in the transport cycle. Studies of the mechanism of  $\text{Na}^+ \text{-H}^+$  exchange in renal brush border membranes have established that extravesicular protons inhibit  $\text{Na}^+$  uptake by competing for a common binding (transport) site on the carrier protein. Single channel investigations of chloride channels from skeletal muscle sarcoplasmic reticulum have demonstrated that ATP and cyclic AMP activate the channel by stimulating the formation of an open state intermediate with a prolonged open time. The mechanism of activation may involve phosphorylation of glycogen phosphorylase which is bound to the SR membrane as an extrinsic protein. Direct visualization of plasma membrane domains in human skin fibroblasts by fluorescence microscopy has been accomplished by selective labelling of the cell membrane with fluorescent phospholipids. Comparison of the labelling patterns in fibroblasts from young and old patients indicate that the domains enlarge during aging secondary to loss of the barriers that surround them.

**Vasculature and Aging.** An explant technique has been developed for isolating vascular endothelial cells from rat thoracic aorta. Positive identification of the cells was achieved by demonstrating a normal proliferative response to endothelial cell growth factor and by immunofluorescent staining with human Factor VIII antiserum. The formation of capillary-like structures by human umbilical endothelial cells (HUVEC) grown in culture on extracellular matrix proteins was stimulated by phorbol ester and inhibited by 8-BrcAMP. Down-regulation of the response to phorbol ester demonstrated that activation of protein kinase C is not essential for the differentiation of HUVEC into these tube-like structures. A method for obtaining freshly-isolated vascular smooth muscle cells from rat tail artery has been developed.  $\text{K}^+$ -induced depolarization of these cells produced an increase in intracellular  $\text{Ca}^{2+}$  and cell shortening which was reversible and could be repeated without loss of effect. Epinephrine elicited a similar response, but the effects were not repeatable, indicating the presence of down-regulation.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00226-08 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Excitation-Contraction Mechanisms in Isolated Cardiac Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

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## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins University

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2

## PROFESSIONAL:

1.6

## OTHER:

0.4

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Two general modes of amplitude modulation of the cardiac contraction are a variation (a) in the number of  $\text{Ca}^{2+}$  ions made available to bind to the myofilaments during the transient increase in cytosolic calcium concentration ( $\text{Ca}_i$ ) following excitation and (b) in the extent of myofilament displacement or force production in response to a given  $\text{Ca}_i$  transient. In order to determine the extent to which a change in the twitch contraction amplitude in intact cardiac cells or muscle is due to either mechanism contraction needs to be assessed simultaneously with measurements of the  $\text{Ca}_i$  transient. A direct assessment of the relationship between  $\text{Ca}_i$  and cell length, and thus myofilament length, can be made in the absence of external mechanical loading in individual isolated cardiac cells. We have designed a method to simultaneously measure contraction and  $\text{Ca}_i$ , as reported by the fluorescent  $\text{Ca}^{2+}$  probe, indo-1 in individual cardiac cells to examine the relationship between  $\text{Ca}^{2+}$  and contraction. During relaxation of the twitch contraction originating from slack length under a given set of conditions, a unique relation exists between cell length and  $\text{Ca}_i$  during twitches that vary in their individual amplitudes manifest as a single trajectory in the cell length- $\text{Ca}_i$  or indo-fluorescence phase plane diagrams. This  $\text{Ca}_i$ -length relationship during electrically stimulated twitches is steeper than that described by peak contraction amplitude versus peak  $\text{Ca}_i$  relationship same as that due to increases in  $\text{Ca}_i$  and contractions elicited via the abrupt and transient application of caffeine or by "tetanization" of the cell in the presence of ryanodine. This unique relationship between  $\text{Ca}^{2+}$ -dependent fluorescence and length shifts appropriately in response to perturbations that have previously demonstrated to alter the steady-state myofilament  $\text{Ca}^{2+}$  sensitivity in skinned cardiac fibers. Thus, the  $\text{Ca}_i$  cell length trajectory during the relaxation phase of contraction appears to define a quasi-equilibrium of cytosolic  $[\text{Ca}^{2+}]$  and myofilament  $\text{Ca}^{2+}$  binding and may be used to assess the myofilament  $\text{Ca}^{2+}$  response during the twitch contraction in single cardiac myocytes.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00228-07 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Age-Associated Changes in Cardiac Rhythm and Conduction

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	E. Sheffrin	Computer Scientist	LSB, NIA

## COOPERATING UNITS (if any)

St. Louis University, Division of Cardiology (H. Kennedy)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.2

## PROFESSIONAL:

0.1

## OTHER:

0.1

## CHECK APPROPRIATE BOXES)

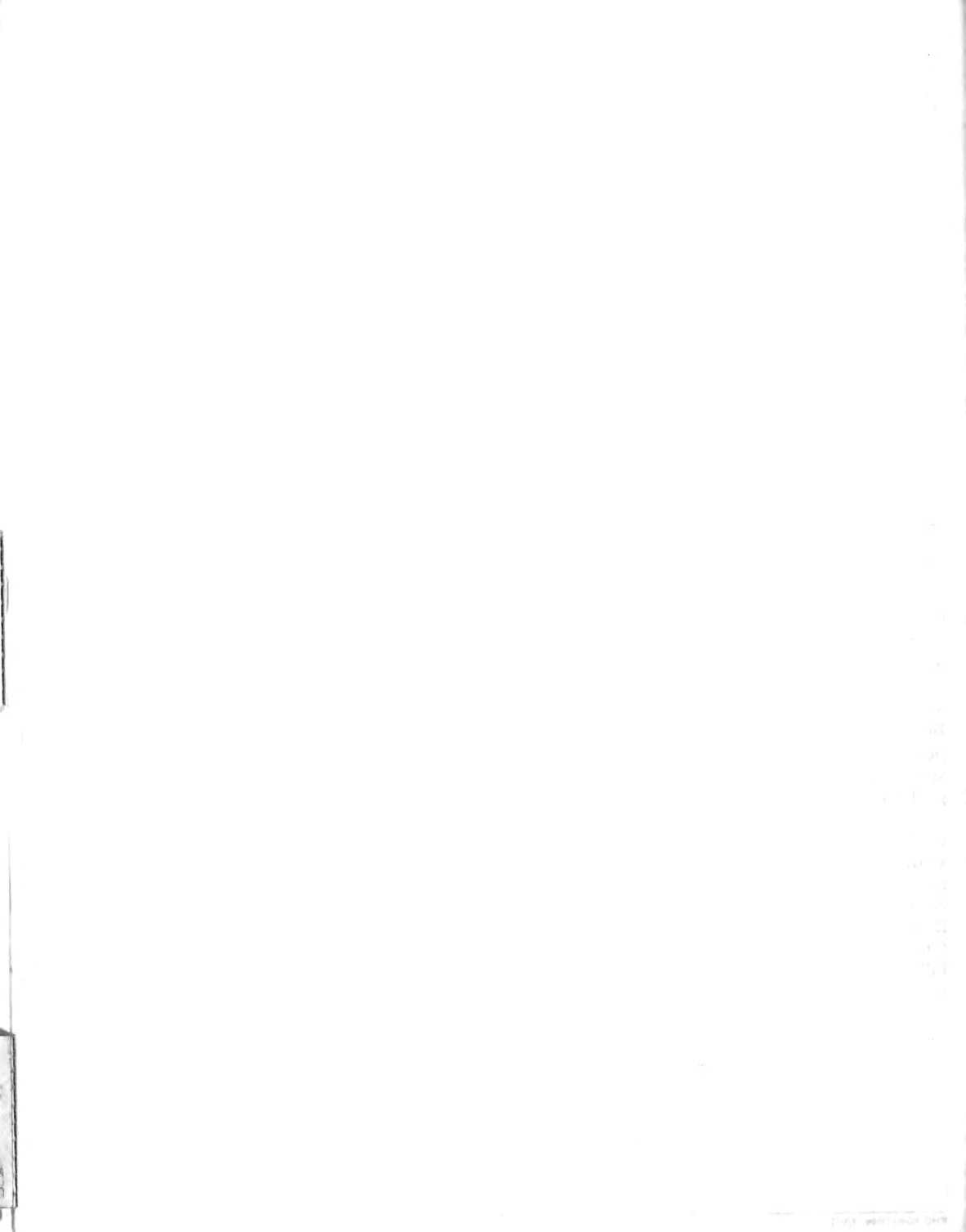
- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A. To determine the site of the PR interval prolongation associated with aging, we performed signal averaged high resolution surface ECGs in 161 clinically healthy Baltimore Longitudinal Study of Aging (BLSA) volunteers with normal atrioventricular (AV) conduction. An increase in PR interval with age was found in both sexes and was localized proximal to the His bundle depolarization but distal to the P wave inscription, suggesting block within the AV junction; a similar qualitatively similar but more pronounced delay was noted proximal to the His bundle in 7 older men with first degree AV block.

B. We have determined the prevalence and significance of exercise-induced frequent or repetitive ventricular ectopic beats (VEB) in apparently healthy BLSA volunteers. Between 1974 and 1984, 80 of 1160 such asymptomatic subjects developed frequent VEB ( $> 10\%$ ) or salvos ( $> 3$  in a row) on at least one maximal treadmill exercise test. These 80 subjects were significantly older than the larger group without such exercise-induced VEB ( $63.8 \pm 12.5$  vs  $50.0 \pm 16.1$ ,  $p < .0001$ ). Only 9 of 80 (11%) demonstrated an ischemic ST segment response to exercise. Over a mean followup of 4.6 years; only 8 cardiac events have occurred versus 10 events in 80 age- and sex-matched control subjects without such complex exercise-induced VEB ( $p = \text{NS}$ ).

C. The prognostic significance of 24-hr ambulatory ECG recordings was assessed in 100 healthy BLSA volunteers  $\geq 60$  years old. Over a mean followup of 10 years, coronary events (CE) developed in 10 subjects. The prevalence and complexity of both supraventricular (SV) and ventricular (V) ectopic beats were similar in the groups with and without CE. However, CE occurred in 2 of 5 subjects (40%) with flat or downsloping ST segment depression  $\geq 1.0$  mm versus only 8 of 95 (8%) without such ST changes.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00231-06 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Regulation of Energy Metabolism

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R. Hansford Chief, EMBS LCS, NIA

Others: B. Hogue Chemist LCS, NIA  
C. Z. Fan Visiting Fellow (EOD 6/1/90) LCS, NIA  
K. Vandegaer Guest Scientist LCS, NIA

## COOPERATING UNITS (if any)

Cardiology Division, Department of Medicine, Johns Hopkins University  
(R. Weiss and G. Gerstenblith).

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Energy Metabolism and Bioenergetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

0.8

## OTHER:

0.6

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is designed to explore the regulation of energy provision by the process of oxidative phosphorylation and the changes which occur as a function of senescence and of disease-states. Particular emphasis is placed upon the control of substrate oxidation at the level of mitochondrial dehydrogenases. This year, we have asked the following questions. (1) What is the effect of the activation of 2-oxoglutarate dehydrogenase and pyruvate dehydrogenase by Ca ions on the proton-electrochemical gradient maintained by rat heart mitochondria? We have approached this by measuring the mitochondrial membrane potential, the largest component of the proton gradient, using a potential-sensitive fluorescent dye, rhodamine 123. (2) What is the impact of senescence upon the activity of the mitochondrial isozyme of creatine kinase in rat heart? This enzyme forms part of the shuttle whereby ATP is made available at the myofibrils in an efficient manner, and its activity has been shown to be diminished in experimentally-induced hypertrophy. (3) Is mitochondrial energy transduction a limiting factor in the diminished contractile performance which is seen in a genetically-determined cardiomyopathy, viz. the BI0 14.6 strain of the Syrian hamster? If so, is there specifically a defect in mitochondrial pyruvate oxidation, associated with altered Ca ion homeostasis by mitochondria in this model? (4) What is the role of substrate-level phosphorylation by glycolysis in allowing tissue survival following cardiac ischemia? Specifically, what factors control the activity of glycogen phosphorylase in low-flow ischemia and upon subsequent reperfusion of the myocardium?





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00243-04 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Spontaneous  $\text{Ca}^{2+}$  Release in the Intact Heart During Ischemia and Reflow

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: H. A. Spurgeon Physiologist LCS, NIA  
M. C. Capogrossi Medical Officer LCS, NIA  
M. D. Stern Guest Researcher LCS, NIA  
P. Blank IPA LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Medical Institutions

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.5

## PROFESSIONAL:

2.2

## OTHER:

0.3

## CHECK APPROPRIATE BOXES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Spontaneous, asynchronous, myocardial calcium oscillations, have been attributed to calcium-dependent calcium release from the sarcoplasmic reticulum (SR) and exhibit a periodicity which depends upon the extent of cell calcium loading. In thin excised cardiac muscle the inhomogeneous contractile motion caused by the spontaneous oscillations phase modulates a laser beam passed through thin excised cardiac muscle, producing intensity fluctuations in the scattered light (SLIF). In the present project we measured intensity fluctuations of 633 nm laser light backscattered from the epicardial surface of isolated, perfused rat and rabbit hearts. The frequency of SLIF was increased by maneuvers that raise intracellular calcium. SLIF were abolished by removal of extracellular calcium with ethylene glycol-bis ( $\beta$ -aminoethyl ether)-N,N,N',N'-tetraacetic acid and by blockade of SR calcium release by ryanodine. SLIF were not accompanied by any surface electrocardiogram and were not abolished by 144 mM extracellular potassium. SLIF were absent in rabbit hearts under base-line conditions but could be provoked by calcium loading using zero potassium and ouabain. Thus, SLIF monitors the microscopic motion caused by intracellular calcium oscillations in the intact heart. Delayed recovery of contractile function after myocardial ischemia may be due to increased calcium loading. To examine this potential mechanism, SLIF were studied in isolated atrioventricularly blocked rat hearts during and after 60 min of ischemia at 30°C. After reperfusion developed pressure evidenced a small recovery but then fell abruptly. This was accompanied by an increase in end-diastolic pressure to  $37 \pm 5$  mm Hg and a fourfold increase in SLIF, to  $252 \pm 58\%$  of baseline. In another series of hearts initial reperfusion with calcium of 0.08 mM prevented the SLIF rise and resulted in improved developed pressure ( $74 \pm 3\%$  of control), and lower cell calcium ( $5.9 \pm 3$  vs  $10.3 \pm 1.4$   $\mu\text{mol/g}$  dry wt). Thus, during reperfusion delayed contractile recovery can be attributed, in part, to an adverse effect of calcium loading which can be indexed by increased SLIF occurring at that time.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00247-04 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Detection and Prognosis of Silent Myocardial Ischemia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Cardiologist	LCS, NIA
Others:	A. Zonderman	Senior Staff Fellow	LPC, NIA
	P. Costa	Chief	LPC, NIA
	E. G. Lakatta	Chief	LCS, NIA
	E. Shefrin	Computer Scientist	LSB, NIA
	L. Brant	Mathematical Statistician	LSB, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital, Baltimore (G. Gerstenblith,  
L.Becker, M.L. Weisfeldt), Akron Cardiology Consultants, Ohio (R. Josephson)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

0.6

## OTHER:

0.9

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among 726 apparently healthy Baltimore Longitudinal Study of Aging (BLSA) men and women who have undergone serial maximal exercise testing since 1969, the risk of future cardiac events was compared in those whose initial test was positive (Group I), those who converted from negative to positive (Group II and those who remained negative over a 6.4 year mean follow-up (Group III). By proportional hazards analysis, Groups I and II had a nearly identical enhanced risk of a cardiac event (RR of 2.78 and 2.72 respectively) compared to Group III subjects. Thus, in asymptomatic volunteers, serial conversion from a negative to a positive exercise ECG has a similar predictive value for a future coronary event as an initially positive ECG response.

To separate the effects of age and silent myocardial ischemia (SI), on the left ventricular (LV) response to maximal upright cycle ergometry, we compared 3 groups: 8 clinically healthy older men (mean age = 76) with prior abnormal ECG and thallium scan (TS) responses to maximal treadmill exercise (OSI); 16 age-matched men with normal ECG and TS responses (OC); and 21 young (mean age = 33) controls (YC). At rest LV ejection fraction (EF), end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were similar in the 3 groups. With cycle exercise LVEF increased markedly in the YC, less in the OC and least in the OSI. In contrast, exercise-induced LV dilatation (increased (ESVI) was most pronounced in the OSI with a lesser increase in the OC; EDVI actually declined below baseline values by maximal effort in the YC. Thus, age-related cardiac dilatation and blunted EF response to upright cycling are exaggerated in older subjects with exercise-induced SI.

Combined into Z01 AG 00228-07 LCS.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00249-04 LCS

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular and Subcellular Calcium Ion Homeostasis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R. G. Hansford Chief, EMBS LCS, NIA

Others: B. Hogue Chemist LCS, NIA

COOPERATING UNITS (if any)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Energy Metabolism and Bioenergetics Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1

PROFESSIONAL:

0.5

OTHER:

0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects

☐ (b) Human tissues

☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of calcium ion concentration, within the cytosol and other cell compartments, and allow perturbations in calcium in response to hormones and neurotransmitters. This year we have investigated the magnitude of the magnesium ion gradient across the mitochondrial membrane and its regulation. This is part of our ongoing study of the regulation of dehydrogenase activity by calcium ions, as the pyruvate and 2-oxoglutarate dehydrogenases are activated by intramitochondrial calcium, with a sensitivity that depends upon the magnesium ion concentration. Intramitochondrial free magnesium was measured by use of the newly-available fluorescent chelating agent Mag-fura, and a dual-excitation spectrofluorimeter. It was found to be in the range of 0.3 to 2 mM, depending on the presence of extramitochondrial magnesium and adenine nucleotides: both ATP and ADP increased mitochondrial free magnesium. Polyamines, e.g., spermine, also increased magnesium, in a process which was dependent on extramitochondrial free calcium. In addition, exposure of mitochondria to free calcium ion concentrations which are plausible for activated cells (0.5 to 1 micromolar) gave rise to large increases in free intramitochondrial magnesium: this may form part of the mechanism whereby elevated cytosolic calcium raises the fraction of active, dephospho pyruvate dehydrogenase in the mitochondria.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00256-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Myocardial Reserve and Calcium Tolerance in the Cardiomyopathic Hamster

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: O. Hano Guest Researcher LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital, Baltimore  
(E. Kasper, H.F. Weisman)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1

## PROFESSIONAL:

0.9

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

While the cardiomyopathic hamster (CMH), B1014.6 strain, develops congestive heart failure with aging, the evolution of compromised myocardial reserve, calcium intolerance, and response to catecholamines prior to overt failure remains to be fully understood and is investigated in this project. We used hearts from 28-52 day old male CMH and age-matched F1B strain control (C) hearts. Isolated, isovolumic and AV blocked hearts were perfused with Hepes buffer at constant pressure and stimulated at 2 Hz at 37°C to investigate the effects of (1) an increasing in bathing [Ca<sup>2+</sup>] (1-10 mM; n = 10 of each), β-adrenergic (isoproterenol, 1 nm - 1 μM; n = 10 of each), (3) α-adrenergic (phenylephrine, 0.1 - 10 μM; n = 10 of each) agonists, and (4) Ca<sup>2+</sup> channel agonist (BAYK8644, 5 nm - 1 μM; n = 10 of each) on contractile properties. In CMH, the peak developed pressure response saturates at a significantly (p < 0.001) smaller developed pressure and declines from maximum occurs at a significantly lower concentrations of α- or β-agonist, Ca<sup>2+</sup> channel agonist or of perfusate [Ca<sup>2+</sup>] compared to control. The rise in end-diastolic pressure with increasing in drug or perfusate [Ca<sup>2+</sup>] concentration in CMH is also significantly (p < 0.001) greater than control. These results suggest that myocardium shows enhanced response to Ca<sup>2+</sup> per se, and also that myocardial cell Ca<sup>2+</sup> loading in response to catecholamines is greater in CMH than in C hearts.

Combined into Z01 AG 00243-04 LCS.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00257-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Mechanism of Oxidant-Induced Intracellular Calcium Loading in Cardiac Myocytes**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H. S. Silverman	Sr Staff Fellow	LCS, NIA
Others:	W. duBell	IRTA Fellow	LCS, NIA
	M. Ninomiya	Guest Researcher	LCS, NIA
	M. D. Stern	Guest Researcher	LCS, NIA
	E. Lakatta	Chief	LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

1.3

## OTHER:

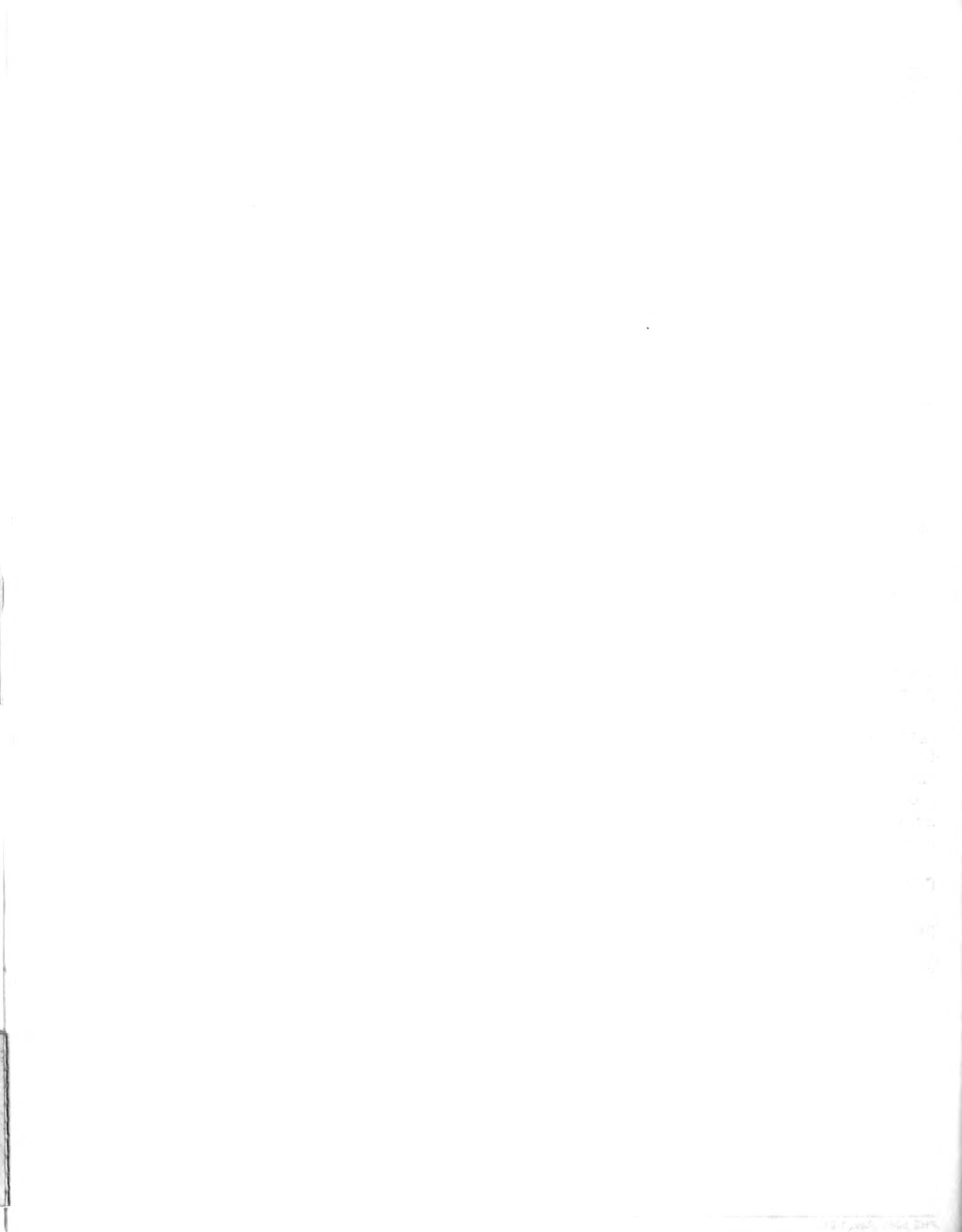
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## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cardiac myocyte injury occurring at reperfusion following a period of ischemia likely results in part from intracellular calcium loading which may be due to the effects of reactive oxygen species which are generated at reperfusion. We previously established that oxygen derived free radicals cause calcium loading and injury in isolated myocytes exposed to an exogenous hydroxyl radical generating system. The present study focuses on the mechanism of radical induced calcium loading in adult rat cardiac myocytes. During exposure to hydrogen peroxide and iron (generates reactive hydroxyl radical) single myocytes demonstrated a transient increase in twitch amplitude following electrical field stimulation and a progressive shortening of diastolic cell length consistent with intracellular calcium loading. Aftercontractions later developed and finally the cell became inexcitable and underwent contracture. Cytosolic calcium, measured with the fluorescent probe indo-1, rose following the administration of the radical generating system. The cellular action potential, monitored with whole-cell clamp techniques, demonstrated marked progressive plateau prolongation without depolarization of the resting potential. Progressive cell shortening and twitch amplitude augmentation were prevented by stimulating the cell under voltage clamp with fixed duration depolarizations. Unstimulated cells failed to demonstrate progressive cell shortening prior to the abrupt onset of contracture. The currents underlying the prolongation of the action potential were studied. A progressive decrease in the magnitude of the calcium current was noted during radical exposure.  $I_{K1}$ , the inwardly rectifying  $K^+$  current, was inhibited and likely contributes to action potential prolongation, which ultimately leads to cellular calcium loading.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00258-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cytosolic Calcium Modulation of the Action Potential

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. duBell	IRTA Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA

## COOPERATING UNITS (if any)

Department of Biology, University of Turku, Finland (A. Talo); Department of Physiology, University of Leeds, England (M. Boyett)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.8

## PROFESSIONAL:

0.7

## OTHER:

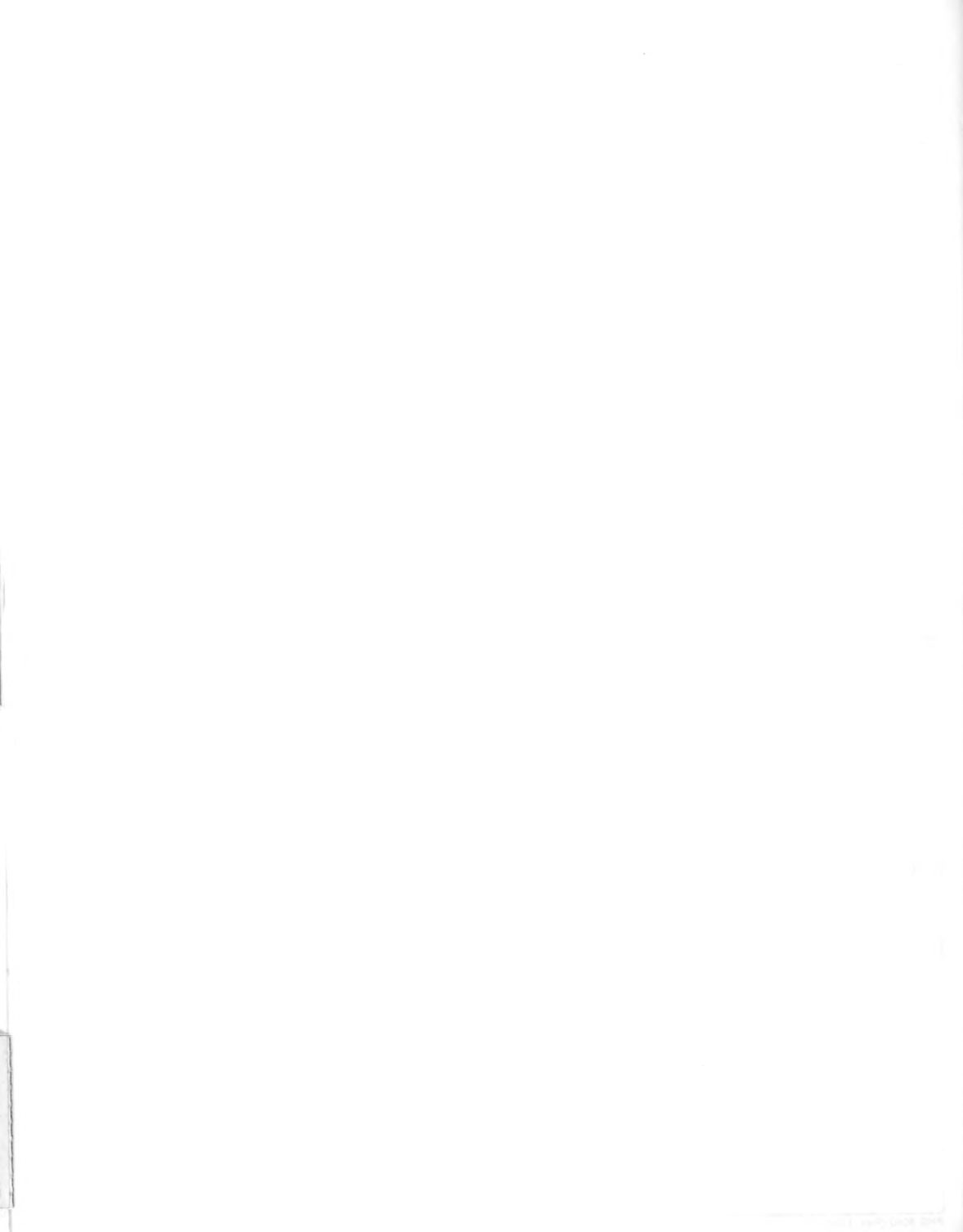
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## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The role of the cytosolic Ca (Ca<sub>i</sub>) transient in determining the configuration of the cardiac action potential was further investigated. For this purpose, rat ventricular myocytes loaded with the Ca<sup>2+</sup>-sensitive fluorescent dye indo-1 were used. Myocytes were loaded with either 1) the acetoxymethyl ester of indo-1 (indo-1 AM), which provides qualitative information about changes in the Ca<sub>i</sub> transient or 2) the Ca<sup>2+</sup>-sensitive, free acid form of indo-1, which allows intracellular Ca<sub>i</sub> to be quantified. The magnitude of the Ca<sub>i</sub> transient was graded by various physiological and pharmacological interventions and membrane voltage or current was recorded using patch-type microelectrodes. Earlier work in indo-1 AM loaded cells had shown that phase-plane loops of membrane potential (V<sub>m</sub>) vs indo-1 ratio from a stimulus train conformed to a common trajectory during the slow tail of repolarization, despite a beat-dependent decrease in the magnitude of the Ca<sub>i</sub> transient. It was found that phase-plane loops of the V<sub>m</sub> vs. indo-1 ratio from spontaneous diastolic Ca<sub>i</sub> oscillations also conformed to this trajectory. Experiments with indo-1 free acid, which was incorporated into the cell by inclusion in the microelectrode filling solution, showed that in rested beats peak Ca<sub>i</sub> can exceed 2 μM and then decrease to 0.4 - 0.6 μM in the steady state. Evidence was found that both electrogenic Na/Ca exchange and a Ca<sup>2+</sup>-dependent ion channel current may participate in the modulation of the cardiac action potential by the Ca<sub>i</sub> transient.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00259-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Opioids Increase  $IP_3$  and Cytosolic  $Ca^{2+}$  in Cardiac Myocytes and Neurons

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. Ventura Guest Researcher LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA  
M. C. Capogrossi Medical Officer LCS, NIA

## COOPERATING UNITS (if any)

Department of Biochemistry, University of Bologna Medical School, Bologna, Italy

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1

## PROFESSIONAL:

0.8

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Opioid peptides modulate neurotransmitter release and myocardial contraction. However, the cellular mechanisms underlying their effects are not known. In particular, their effects on cytosolic  $Ca^{2+}$  ( $Ca_i$ ) homeostasis are still largely undefined. The present study shows that in rat ventricular myocytes loaded with the  $Ca^{2+}$  probe indo-1, the  $\kappa$  opioid receptor agonist (trans-(dl)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclo-hexyl]-benzeneacetamide) methane sulfonate hydrate (U-50,488H) causes a transient increase followed by a monotonic decrease in the amplitude of the twitch and of the  $Ca_i$  transient, indexed as the 410/490 nm ratio of indo-1 fluorescence. Under similar conditions the  $\delta$  opioid leucine-enkephalin decreases twitch and  $Ca_i$  amplitudes without causing a transient increase in either signal. In the absence of electrical stimulation U-50,488H and leucine-enkephalin slowly increase  $Ca_i$  or cause  $Ca_i$  oscillations and eventually abolish the caffeine-triggered  $Ca_i$  transient. This occurs in both myocytes and neuroblastoma-2a cells. These effects of the U-50,488H and leucine enkephalin on both cell types are prevented by the  $\kappa$  and  $\delta$  opioid receptor blockers (-)-N-(3-Furylmethyl)- $\alpha$ -normetazocine methansulphonate (Mr 1452) and naloxone. In cardiac myocyte suspensions U-50,488H and leucine-enkephalin both cause a rapid and sustained increase in inositol-1,4,5-trisphosphate ( $IP_3$ ). The peak effect of the  $\kappa$  agonist on  $IP_3$  production is of greater magnitude and occurs with a faster time course than that of the  $\delta$  opioid and may account for the different effects of these peptides on the  $Ca_i$  transient in electrically stimulated cardiac myocytes. Thus, both in cardiac cells and neurons  $\kappa$  and  $\delta$  opioid receptors appear to be coupled to phosphatidylinositol turnover leading to  $Ca^{2+}$  release from intracellular stores.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00260-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Novel Positive Cardiac Inotropic Agents

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	C. Ventura	Guest Researcher	LCS, NIA
Others:	O. Hano	Guest Researcher	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	R. Miller	Biologist DOD 8/89	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA

## COOPERATING UNITS (if any)

E. Merck, Darmstadt, West Germany (M. Klockow)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.8

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

All positive inotropic agents that are available for clinical use exercise their effect predominately via an increase in cell calcium loading. However once the myocardial preparation has reached its peak contractile response a further increase in cell calcium loading is associated initially with a plateau and then with a decline in the inotropic state of the muscle, an increase in diastolic tone, aftercontractions and arrhythmias. This condition which has been defined as "calcium overload" represents the limiting factor in the clinical use of positive inotropic agents. Thus, it is desirable to develop drugs that increase the contractility of the heart via an enhancement in myofilament responsiveness to calcium rather than by increasing the extent of cell calcium loading. We tested the effect of novel thiadiazinone derivatives (designed by E. Merck, Darmstadt, FRG) that vary in potency (1) to sensitize skinned myocardial fibers to  $\text{Ca}^{2+}$ :  $\text{EMD } 54622 \geq 53998 > 54650$ , and (2) to inhibit phosphodiesterase III in cell homogenates ( $54650 \geq 53998 > 54622$ ). We determined whether differential  $\text{Ca}^{2+}$ -myofilament effects are expressed in intact guinea pig cells, bathed in Hepes buffer ( $23^\circ\text{C}$ ) and loaded with the fluorescent  $\text{Ca}^{2+}$  probe, indo-1. Our results show that the steepness of relationship among twitches and indo-1 fluorescence transients measured across drug dose varies as  $54622 > 53998 > 54650$ . Thus, differential modifications of the myofilament  $\text{Ca}^{2+}$  response in intact cells can be effected via molecular modifications of thiadiazinone that enhance its potency to sensitize myofilaments to  $\text{Ca}^{2+}$ .





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00261-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Novel Single Cell Techniques in the Study of Myocardial Contractility, Adaptation, and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S. J. Sollott Medical Staff Fellow LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.8

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Novel single cell techniques have been developed which permit the simple and reproducible characterization of the length/load-dependent contractile performance of single adult mammalian heart cells, with the simultaneous measurement of the transient change in cytosolic calcium, as indexed by changes in indo-1 fluorescence. Cells are embedded in a transparent, elastic polymer matrix which enables reversible gradations (via matrix stretch) in resting and stimulated-auxotonic-contraction length. Length-dependent  $Ca^{2+}$  myofilament activation and load dependent relaxation have been demonstrated for the first time in single mammalian ventricular myocytes with this technique. The utility of various indices derived from edge motion measurements, including edge acceleration and relative impulse of the force, have been applied to this technique for the first time and have been demonstrated as valid indices of "contractility," in lieu of actual measured force. Techniques have also been developed which permit the non-destructive, selective loading of calcium fluorescent indicators (such as indo-1 "free acid") into the myoplasm of large numbers of heart cells, overcoming past limitations of nonselective organelle dye-loading (especially mitochondria) complicating the use of membrane-permeant dye-ester derivatives and preventing rigorously-valid  $Ca^{2+}$  calibration. Work is proceeding along these lines to perfect a routine, practical method to obtain validly calibrated myoplasmic  $Ca^{2+}$  transients for these contractility studies. Viable human heart cells from atrial and ventricular chunk surgical specimens are successfully isolated via enzymatic techniques in our lab on a regular basis, and will be studied by these techniques. A growing body of evidence supports the concept that cardiac adaption to hemodynamic stress is reduced with aging, playing a significant role in the pathogenesis of human disease. However, the underlying molecular mechanisms and factors regulating cardiac growth and resulting myocardial function are incompletely understood. Techniques are thus being developed in this isolated single heart cell model to correlate graded cell stretch and loading,  $Ca^{2+}$  and age, with contractile function, the expression of proto-oncogene and heat shock protein mRNA, and changes in contractile protein gene isoform expression (i.e. coding for  $\alpha$  skeletal actin,  $\beta$  myosin heavy chain), via in situ hybridization.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00262-02 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## pH Regulation in Cardiac Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	P. S. Blank	IPA	LCS, NIA
Others:	H. Silverman	Senior Staff Fellow	LCS, NIA
	M. D. Stern	Guest Researcher	LCS, NIA
	M. C. Capogrossi	Medical Officer	LCS, NIA
	R. G. Hansford	Chief, EMBS	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	O. Chung	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.5

PROFESSIONAL:

0.5

OTHER:

0

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Physiological studies have been aided by the use of intracellular indicators. Indicators for intracellular calcium and pH are used in monitoring physiological and pathophysiological properties of isolated cardiac myocytes and intact cardiac tissue. This project developed a novel time resolved system for cytosolic pH measurements using the recently synthesized intracellular pH indicator, SNARF-1, seminaphthorhodalfleur, with simultaneous measurements of cell length.

The emission spectrum of SNARF-1 contains two-well separated emission peaks at 590 and 640 nm. This feature allows the indicator to be used in the single excitation, dual emission, ratio mode; analogous to the calcium indicator, INDO-1. SNARF-1 is available in both the free acid form and as a cell permeant acetoxymethyl ester. We have found that isolated cardiac myocytes are easily loaded with ester, and have the following characteristics: 1) a consistent intracellular calibration can be obtained, 2) the contractile properties are essentially unchanged in the presence of the indicator, 3) the indicator is present primarily in the cytosol (95% to 100%) with virtually no partitioning into the mitochondria, 4) the indicator is retained for several hours at room temperature, and 5) steady-state pH and transient changes in pH are easily monitored. Changes in pH can be monitored during important physiological and pathophysiological perturbations. The initial applications of the SNARF-1 system include 1) pH regulation and changes in contractile state during anoxia, acidosis, and anesthesia and 2) receptor mediated changes in contractile state.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00263-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

**Mechanism of Post-Hypoxic Impaired Myocyte Relaxation**

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H. S. Silverman	Sr Staff Fellow	LCS, NIA
Others:	P. S. Blank	IPA	LCS, NIA
	H. Miyata	Visiting Fellow	LCS, NIA
	H. S. Spurgeon	Physiologist	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	M. S. Stern	Guest Researcher	LCS, NIA

COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

2

PROFESSIONAL:

1.8

OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
 ☐ (b) Human tissues
 ☒ (c) Neither
- ☐ (a1) Minors
 ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Striking changes in the time course of myocardial contraction have been documented during and following brief periods of ischemia or hypoxia. These studies have been conducted in whole tissue preparations and have allowed only partial delineation of the mechanisms underlying these changes in mechanics. Recent technical advances have allowed the more detailed study of these events at the single cell level. A special chamber, developed in our laboratory, was employed to study contraction in single cells during and after brief periods of profound hypoxia ( $pO_2 < .02$  torr). Rat ventriculocytes, loaded with the calcium-sensitive fluorescent probe indo-1, showed no early failure of contraction upon exposure to hypoxia, however marked changes in the timing of cell contraction and relaxation occurred early during hypoxia and at reoxygenation following brief hypoxia (10 minutes at 23° C). During hypoxia time to peak contraction (TPK) and time to 50% relaxation (RT50) were abbreviated without a significant change in the time to 90% relaxation (RT90). The timing of the calcium transient was unaffected. At reoxygenation TPK, RT50 and RT90 were markedly prolonged again without any change in the timing of the calcium transient. Simultaneous measurement of the action potential and contraction in current-clamped cells showed similar mechanical changes without a change in the AP. We have recently documented a transient rebound intracellular alkalosis (using the pH sensitive fluorescent probe SNARF-1) which occurs at reoxygenation and may contribute to the slowing of relaxation seen at reoxygenation by slowing myofilament relaxation kinetics.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00264-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Left Ventricular Volumes in Normal Man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	J. L. Fleg	Staff Cardiologist	LCS, NIA
	D. Drinkwater	Visiting Fellow	LCP, NIA
	S. Fortney	Guest Scientist	LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital (D. Renlund, S. Schulman,  
G. Gerstenblith, L. Becker)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.0

## PROFESSIONAL:

1.2

## OTHER:

1.8

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A. To determine the extent to which L. ventricular end-systolic volume (ESV) "follows" the end-diastolic volume (EDV) response to various perturbations, we measured EDV and ESV by gated blood pool scan in 119 healthy, rigorously screened BLSA volunteers ages 21-81 yr in response to postural shift, during graded upright cycle exercise in an additional 31 subjects who exercised during  $\beta$ -adrenergic blockade (propranolol 0.15 mg/kg) and in 18 older men during lower body negative pressure. Multiple regression analysis showed that the changes in ESV ( $\Delta$ ESV) during a postural shift or during graded exercise was highly statistically correlated with the change in EDV ( $\Delta$ EDV) that occurred ( $r^2$  ranged from 0.34 to 0.49, correlation is positive) regardless of age, sex, or exercise workload. Thus, diverse perturbations of left ventricular EDV caused by postural stress, cycle exercise and  $\beta$ -adrenergic blockade result in parallel changes in ESV.

B. We tested whether vigorous endurance training (ETR) in older men prevented the normal age-related decreased peak filling rate (PFR) in EDV/sec and increased time to PFR, (TPFR) in msec, by comparing rest and exercise gated blood pool scans (20 frames/RR) from 12 ETR senior master athletes (O-ETR)(mean age=65.4,  $VO_2$  max (ml/kg/min)=51.5), 12 sedentary older men (O-C) (age=66.8),  $VO_2$ max=32.3) and 8 young men (Y)(age=33.1). Both O-ETR and O-C had negative exercise thallium scans. Data =  $\pm$  S.D.

	Rest	50 Watt	100 Watt
PFR,O-ETR	2.11 $\pm$ .38	3.74 $\pm$ .58	4.57 $\pm$ 1.06
PFR,O-C	2.13 $\pm$ .53	4.16 $\pm$ .73	5.53 $\pm$ 1.73
PFR,Y	3.91 $\pm$ .91*	5.69 $\pm$ .83*	6.82 $\pm$ 1.64*

\*p < 0.01 vs O-ETR and O-C; +p < 0.01 vs O-ETR.

Heart rate adjusted PFR, as well as TPFR also did not differ between O-Ex and O-C. Thus, ETR does not prevent the altered diastolic filling characteristics associated with normal aging. In a related study,  $\beta$ -adrenergic blockade with propranolol attenuated the exercise-induced increase in PFR in healthy young men (age = 30) but not in healthy older men (age = 64).





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00265-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Effects of Age and Gender on Exercise Cardiac Performance

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: F. O' Connor Chemist LCS, NIA  
E. G. Lakatta Chief LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital (G. Gerstenblith, L. Becker, V. Coombs, J. Clulow)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

4

## PROFESSIONAL:

1.5

## OTHER:

2.5

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A. To determine the independent effects of age and gender on the left ventricular ejection fraction (LVEF) response to upright cycle exercise, we performed gated blood pool scans at rest and maximal upright cycle exercise in 93 men and 49 women ages 23-86 yrs free of heart disease by history, physical exam, rest and exercise ECG and if >40 yr old, exercise thallium scan. The change in LVEF ( $\Delta$ LVEF) from rest to maximal workload (MWL) declined in men from  $22 \pm 6$  units under the age of 40 yrs to  $10 \pm 9$  units if older than 60; corresponding values in women were  $17 \pm 6$  below age 40 and  $3 \pm 10$  above age 60 yrs. The specificity of a  $\Delta$ LVEF  $\geq 5$  units for the absence of coronary artery disease (CAD) was 100% for all subjects younger than 40 yrs but decreased to 70% and 54% respectively in men and women aged 60 and beyond. By multiple regression analysis both age ( $p < .0001$ ) and gender ( $p < .05$ ) were independent determinants of  $\Delta$ LVEF ( $\Delta$ LVEF =  $32.2 - 0.26 \text{ age} - 4.4 \text{ sex}$ ) but only age ( $p < .0006$ ) predicted absolute LVEF at MWL. Thus, both increasing age and female sex independently diminish  $\Delta$ LVEF in healthy subjects, decreasing the specificity of  $\Delta$ LVEF for CAD.

B. To examine gender differences in exercise hemodynamics in older subjects, we performed gated blood pool cardiac scans at rest and during maximal upright cycle exercise in 45 healthy volunteers  $\geq 60$  years old with normal resting and treadmill ECG and thallium scans. At rest, end-diastolic and end-systolic volume indices (EDVI and ESVI) were larger in men than women ( $77.4 \pm 3.2$  vs  $64.4 \pm 3.3$  ml/M<sup>2</sup>,  $p < .02$  and  $27.7 \pm 1.7$  vs  $19.9 \pm 1.6$  ml/M<sup>2</sup>,  $p < .01$ ) respectively. Resting stroke volume index (SVI), cardiac index (CI), and heart rate (HR) were similar. At maximal workload (MWL) which was  $122 \pm 4.2$  watts in men vs  $79 \pm 5.1$  in women,  $p < .01$ , EDVI ( $87 \pm 3.5$  vs  $74 \pm 4.6$  ml,  $p < .05$ ), SVI ( $63 \pm 2.3$  vs  $53.7 \pm 2.6$  ml,  $p < .01$ ) and CI ( $8.5 \pm 0.3$  vs  $7.4 \pm 0.4$  l/min/M<sup>2</sup>,  $p = .06$ ) were larger in men whereas HR was higher in women ( $147 \pm 4.5$  vs  $137 \pm 2.9$  beats/min,  $p = .06$ ). When older men and women matched for fitness level (MWL of 75-100 watts) were compared, all hemodynamics were similar at rest and at MWL except for the higher HR at MWL in women,  $149 \pm 5.0$  vs  $129 \pm 3.8$  beats/min,  $p < .01$ . Thus, smaller resting and exercise ventricular volumes in older women are mediated by their lower fitness level.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00266-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Ion Transport Mechanisms and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. P. Froehlich	Chief, MBS	LCS, NIA
Others:	J. Kinsella	Research Physiologist	LCS, NIA
	P. Heller	Chemist	LCS, NIA
	E. Koh	Visiting Fellow	LCS, NIA
	E. Yechiel	Visiting Associate	LCS, NIA
	R. W. Albers	Chief, Enzymes Section	LNC, NINCDS

## COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NINCDS, NIH, Bethesda, MD; MAX-Planck-Institut für Biophysik, Frankfurt, Germany (K. Fendler, K. Hartung, E. Bamberg and E. Grell)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Membrane Biology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.75

## PROFESSIONAL:

3.75

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Kinetic investigations of the electrical behavior and enzymatic partial reactions of the ATP-dependent Na<sup>+</sup>K<sup>+</sup> and Ca<sup>2+</sup> pumps have demonstrated that the phosphoenzyme conformational transition is an electrogenic step in the transport cycle. Studies of the mechanism of Na<sup>+</sup>-H<sup>+</sup> exchange in renal brush border membranes have established that extravesicular protons inhibit Na<sup>+</sup> uptake by competing for a common binding (transport) site on the carrier protein. Single channel investigations of chloride channels from skeletal muscle sarcoplasmic reticulum have demonstrated that ATP and cyclic AMP activate the channel by stimulating the formation of an open state intermediate with a prolonged open time. The mechanism of activation may involve phosphorylation of glycogen phosphorylase which is bound to the SR membrane as an extrinsic protein. Direct visualization of plasma membrane domains in human skin fibroblasts by fluorescence microscopy has been accomplished by selective labelling of the cell membrane with fluorescent phospholipids. Comparison of the labelling patterns in fibroblasts from young and old patients indicate that the domains enlarge during aging secondary to loss of the barriers that surround them.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00267-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Vasculature and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. Kinsella	Research Physiologist	LCS, NIA
	L. Cheng	Research Chemist	LCS, NIA
Others:	J. Froehlich	C, MBS	LCS, NIA
	E. Lakatta	Chief	LCS, NIA
	E. Koh	Fogarty Fellow	LCS, NIA
	H. Klineman	Chief, Cell Biol Sec	LDBA, NIDR
	D. Grant	Visiting Fellow	LDBA, NIDR

## COOPERATING UNITS (if any)

Laboratory of Developmental Biology and Anomalies, NIDR, NIH, Bethesda, MD.

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Membrane Biology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.25

## PROFESSIONAL:

2.25

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
 ☐ (b) Human tissues
 ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An explant technique has been developed for isolating vascular endothelial cells from rat thoracic aorta. Positive identification of the cells was achieved by demonstrating a normal proliferative response to endothelial cell growth factor and by immunofluorescent staining with human Factor VIII antiserum. The formation of capillary-like structures by human umbilical endothelial cells (HUVEC) grown in culture on extracellular matrix proteins was stimulated by phorbol ester and inhibited by 8-BrcAMP. Down-regulation of the response to phorbol ester demonstrated that activation of protein kinase C is not essential for the differentiation of HUVEC into these tube-like structures. A method for obtaining freshly-isolated vascular smooth muscle cells from rat tail artery has been developed. K<sup>+</sup>-induced depolarization of these cells produced an increase in intracellular Ca<sup>2+</sup> and cell shortening which was reversible and could be repeated without loss of effect. Epinephrine elicited a similar response, but the effects were not repeatable, indicating the presence of down-regulation.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00268-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Progressive Changes in mRNA of Rat Cardiac Myosin Heavy Chain Genes With Adult Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: L. O'Neill Chemist LCS, NIA  
N. J. Holbrook Chief, UEA LMG, NIA  
J. Fargnoli Senior Staff Fellow LMG, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

0.3

## OTHER:

0.7

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cardiac cell enlargement occurs in response to chronic arterial pressure overload in young rodents and with advanced adult age in normotensive rodents. Cardiac muscle of both senescent and pressure overloaded hearts exhibit a nearly identical pattern of altered cardiac excitation-contraction mechanisms, among which are a reduced contraction velocity, a reduction in the myosin ATPase activity, a marked increase in the expression of the V<sub>1</sub> ( $\beta$  myosin heavy chain, MHC) and a reduction in V<sub>1</sub> ( $\alpha$  MHC) isoforms. In the heart of younger hypertensive adult rodents, this shift in MHC isoforms is due, in part at least, to changes in transcription of  $\beta$  and  $\alpha$  MHC genes. The present study was undertaken to determine whether the marked MHC shift occurring with age between adulthood and senescence is also associated with changes in MHC gene expression. Levels of mRNA coding for  $\alpha$  and  $\beta$  MHC were determined by Northern analysis and dot blots (oligonucleotide probes on pooled RNA purified from 6 hearts each of animals of a broad age range. The mRNA for  $\beta$  MHC increased greater than fourfold from 1 to 24 months, the  $\alpha$  mRNA for  $\alpha$  MHC decreased by a proportional amount. Thus, the phenotypic, biophysical and biochemical cardiac contractile changes with adult aging are, in part at least, transcriptionally regulated.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00269-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effects of  $\beta$ - and  $\alpha$ -Adrenergic Stimulation on Cytosolic pH in Cardiac Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: G. Gambassi Guest Researcher LCS, NIA

Others: H. A. Spurgeon Physiologist LCS, NIA  
 E. G. Lakatta Chief LCS, NIA  
 M. C. Capogrossi Medical Officer LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.8

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Both  $\beta$ - and  $\alpha$ -adrenergic receptor agonists have a positive inotropic effect on the heart. Their action is associated with an increase in the cytosolic  $[Ca^{++}]$ , ( $Ca_i$ ) transient and also with a change in myofilament responsiveness to  $Ca^{++}$ .  $\alpha$ -adrenergic agonists appear to enhance myofilament responsiveness to  $Ca^{++}$  and this effect may contribute to the increase in contractility. In contrast  $\beta$ -adrenergic stimulation of the heart decreases myofilament  $Ca^{++}$  sensitivity and it has been suggested that this effect may contribute to the "relaxing" action of  $\beta$ -adrenergic stimulation. In non-myocardial cells  $\alpha$ -adrenergic stimulation has been shown to increase cytosolic pH ( $pH_i$ ), probably via an increase in phosphatidylinositol turnover leading to protein kinase C mediated activation of  $Na^+/H^+$  exchange. Interventions that increase cAMP can also modulate  $Na^+/H$  exchange and either decrease  $pH_i$  (e.g., epithelial cells) or increase  $pH_i$  (e.g., red blood cells). In the myocardium, myofilament sensitivity to  $Ca^{++}$  is profoundly effected by changes in  $pH_i$  and the contractility of the heart is decreased by acidosis and increased by alkalosis. Thus, we investigated the effect of  $\beta$ - and  $\alpha$ -adrenergic stimulation on  $pH_i$  in myocardial cells. We used ventricular myocytes from the adult rat, loaded with the  $pH_i$  probe SNARF-1 to assess the effect of isoproterenol. Cells in bicarbonate buffer were studied during electrical stimulation and at rest. Isoproterenol increased twitch amplitude and had no effect on  $pH_i$ . In contrast,  $\alpha$ -adrenergic stimulation with phenylephrine and nadolol enhanced twitch amplitude and increased  $pH_i$ . There was a significant correlation between the increase in twitch amplitude and  $pH_i$ . Both effects were antagonized by ethylisopropylamiloride a  $Na^+/H^+$  inhibitor. Thus  $\alpha$  which stimulates phosphatidylinositol turnover increases  $pH_i$  and this may contribute to its positive inotropic action. In contrast,  $\beta$ -adrenergic stimulation, which increases cAMP has no effect on  $pH_i$  in myocardial cells.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00270-01 LCS

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Age Associated Changes in Ventricular-Vascular Coupling

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	P. Vaitkevicius	Clinical Associate	LCS, NIA
	J. Fleg	Staff Cardiologist	LCS, NIA
	S. Austin	Geriatric Fellow	LCS, NIA
	J. Engel	Computer Scientist	LCS, NIA

COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

1.25

## OTHER:

0.25

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The heart and vasculature of normotensive elderly subjects may demonstrate changes of a muted form of hypertension. Left ventricular hypertrophy, a reduction in early diastolic filling, and increased vascular stiffness are features shared by the cardiovascular systems of normotensive elderly and younger hypertensive individuals. This study of ventricular-vascular coupling attempts to determine and correlate age associated changes in left ventricular mass and vascular stiffness. To date arterial pressure wave recordings have been non-invasively obtained from the carotid artery in 142 healthy normotensive BLSA participants and members of the Master Athlete study by means of a transcutaneous tonometer containing a high fidelity Millar micromanometer, pulse wave velocity measurements have been made by simultaneously obtained doppler flow recordings. Carotid pressure wave forms from the first 41 participants have been analyzed to measure the time from the shoulder to peak amplitude (PiP) and the augmentation index (AGI%). The shoulder was determined from the third derivative of the pressure tracing. A late systolic pressure peak and an increase in the pulse wave velocity were noted with advancing age. Both PIP and AGI% correlate significantly with age. Additionally LV mass determination has been made by either M-mode or 2-D echocardiography or magnetic resonance imaging. Determination of mass is pending refinements in the computer software system used for data analysis. Subsequent correlations of LV mass with PIP, AGI%, and PWV are awaiting these modifications. The reliability of tonometric measurements will be established by direct comparison of non-invasive carotid waveforms to invasively obtained aortic pressure contours. Future studies include the use of applanation tonometry to evaluate exercise induced alterations in arterial contour in various age groups.



LMG-IRP-NIA

LN-IRP-NIA



## LABORATORY OF MOLECULAR GENETICS:

### Overview:

#### Unit on Gene Expression and Aging

With age, we lose the ability to adapt to environmental stresses that require a sudden and amplified response. The focus of the Unit on Gene Expression and Aging is the study of genes which are expressed by cells in response to specific toxins, injury, stress, or other conditions deleterious to cells. Our working hypothesis is that these systems protect the organism from damage from environmental factors and that these protective responses become blunted with age. Major attention is directed towards two classes of genes; the heat shock proteins and the *gadd* (growth arrest and DNA damage inducible) genes.

Heat Shock Protein Genes. The heat shock response is a universal response found in cells from bacteria to humans and involves the expression of a specific set of genes which appear to be involved in protecting the cell against a variety of toxic and stressful situations. We have shown that the heat shock response is reduced in old animals exposed to either hyper- or hypo-thermic conditions. In addition, we have shown that a unique member of the HSP70 gene family is specifically expressed in the adrenal gland of rats in response to mild restraint stress, and that this expression declines with age. Current studies are directed toward determining the regulation of this response and characterizing the defect in the old animals.

Genetic Response to DNA damage. DNA damage elicits the expression of many genes. Some of these are directly involved in the repair of the damage while others appear to play protective roles. In lower organisms DNA damage induces a set of genes which are known to be responsible for delaying cell growth and division, presumably to prevent damaged DNA from being replicated. No analogous genes have yet been identified in mammalian cells, but members of this research unit are investigating one such candidate, the *gadd153* gene, whose expression is induced following treatment of cells with agents that damage DNA or inhibit cell growth. Thus, *gadd153* may play an important role in the initiation of growth arrest seen in response to DNA damage as well as other adverse growth conditions. Studies are directed toward understanding the regulation of *gadd153* expression during normal cell growth as well as with senescence and aging, and toward defining the function of the *gadd153* gene product.

We suggest that systems such as the HSP and *gadd153* genes have been selected evolutionarily and are critical for cell survival. Their attenuated expression with age would be expected to leave old cells more sensitive to environmental toxins and degenerative changes.

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## Unit on Cell Proliferation and Aging

### Introduction

The exact causes of aging are as yet undetermined. However, the evidence suggests that aging is a multifactorial process based on random damage to cell components. This damage causes a small fraction of cells in each tissue to be destroyed and a larger fraction to lose a variable amount of function. As the reserve capacity of critical organs is exceeded, the organism shows an exponential increase in morbidity and mortality.

In principle, this process could be blocked or reversed by stimulating parenchymal cells to proliferate, which would increase organ capacity and dilute out damaged molecules in individual cells. Such compensatory hyperplasia is adequate in many situations, such as liver regeneration after surgical resection, but is inadequate with age. Even constantly proliferating tissues, such as skin, show a decrease in such proliferation.

At least three basic mechanisms may contribute to failed proliferation with age: (1) a decrease in positive growth signals; (2) damage to the cellular proliferation machinery; and (3) the presence of proliferation inhibitors inside cells. The goals of this unit are to learn why proliferation is inadequate with age and to apply this knowledge to the restoration of function in aging tissues.

Experimental Approach. We have begun this work by isolating the gene for prohibitin, a novel intracellular antiproliferative protein. Prohibitin is widely expressed in different tissues, highly conserved in evolution, and appears to act in the G1 phase of the cell cycle. Our working hypothesis is that prohibitin is a universal regulator of the cell cycle in all tissues of all organisms, acting to control entry into the DNA synthesis portion of the cycle.

Analysis of Prohibitin Itself. The first phase of this project is necessarily narrow and focuses entirely on prohibitin. The structure of the gene is being determined across a range of species from yeast to man to determine the key features of the protein. Yeast studies will also provide a powerful system for isolating cooperating genes in the pathway of prohibitin action in the cell. We have preliminary evidence for alternative protein forms being produced in the fruit fly; the analysis of these forms should yield further insights into prohibitin control mechanisms. To determine what molecules prohibitin interacts with in the cell, studies are underway with immunocytochemistry, immuno electron microscopy, and immunoprecipitation of prohibitin and the proteins it binds.



Analysis of Prohibitin Interaction with Other Genes. The second phase of this project is much broader and aims to place prohibitin within the larger framework of cell growth control molecules. To this end, we are testing the effect on prohibitin expression of applying negative growth factors, such as transforming growth factor beta and tumor necrosis factor. Also in progress are gene constructs that will allow us to turn prohibitin on and off in cells, so that effects on other intracellular antiproliferative factors such as p53 and the retinoblastoma protein can be analyzed.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00705-05 LMG

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of a gene involved in shutting off cell growth.

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	M.J. Nuell	Senior Staff Fellow	LMG, NIA
	D.A. Stewart	Research Associate	LMG, NIA
	V. Friedman	Fogarty Fellow	LMG, NIA
	C.M. Wood	NRC Fellow	LMG, NIA
	J. J. White	Biologist GS-11	LMG, NIA
	G.A. Owens	Biologist GS-9	LMG, NIA

## COOPERATING UNITS (If any)

Dept. of Virology, Baylor College of Medicine (J.R. Smith)  
Noble Foundation, Ardmore, Oklahoma (J.K. McClung)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

6.9

## PROFESSIONAL:

4.9

## OTHER:

2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A number of laboratories have provided data suggesting that nondividing cells contain intracellular proteins that actively inhibit cell proliferation. In earlier work, we isolated a cDNA for the protein prohibitin based on its preferential expression in nondividing (versus regenerating) liver and the ability of its cognate mRNA to block normal fibroblasts from entering S phase. Prohibitin was shown to be expressed in a wide range of cells; in fibroblasts, it is expressed at a high level in G1 and a low level in S.

We have now cloned a cDNA for prohibitin that encodes the entire protein. Prohibitin is 30 kilodaltons in size with two major domains of secondary structure. The existence of these two domains seems related to the location of prohibitin in the cell, which can be either nuclear or cytoplasmic. Prohibitin genes are highly conserved in evolution, with 75% amino acid identity between the proteins of human and fruit fly. It is therefore a strong possibility that all organisms have a prohibitin equivalent. Prohibitin is a potent negative regulator of cell growth; it can block proliferation in HeLa (cancer) cells.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00719-02 LMG

PERIOD COVERED October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Heat Shock Protein Gene Expression in Response to Stress and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Investigator, LMG, NIA

Others - Michael J. Blake, Senior Staff Fellow, LMG, NIA

Gregory J. Fuelner, IRTA Fellow, LMG, NIA

Darrell D. Norton, Biologist GS-9, LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Behavioral Sciences, Behavioral Physiology Section,  
NIA (Dr. Hal Tatelman and Mark Talan)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

2.75

PROFESSIONAL:

1.75

OTHER:

1.0

CHECK APPROPRIATE BOXES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Heat and a variety of other damaging agents are known to induce the expression of a set of highly conserved proteins known as the heat shock proteins (HSPs). These proteins, which appear to be critical for cellular homeostasis, have been studied extensively in cultured cells, but relatively little is known concerning their expression in vivo. In this project we are examining the expression of HSPs in rodents in response to physiological stresses in vivo. Particularly focusing on the HSP response in aging. Previously, we demonstrated that HSP70 expression was impaired in cultured fibroblasts from aged rats relative to those of young rats. We also demonstrated that HSP70 expression was reduced in aged animals subjected to heat stress in vivo, but the diminished response appeared to be secondary to alterations in thermoregulation. Over the past year we have shown that in mice HSP70 expression is also induced in brown fat (the major heat generating organ) in response to cold stress. Again, an age-related decline in the expression is apparent and appears to be the result of, at least in part, altered thermoregulation. More recently, we have observed that HSP70 is also induced in response to restraint stress in rats. Two important features of this response are that the induction is relatively specific to the adrenal gland and involves the selective expression of one particular gene transcript. These findings along with our previous observations of specific localized HSP70 expression in regions of the brain associated with the neuroendocrine axis suggest a link between this cellular response to stress and the classical hormonal stress response.

LPC-IRP-NIA

LN-IRP-NIA





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00720-01 LMG

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Gene Expression in Chronic Wounds and Aged Cells

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P. I.: George R. Martin, Acting Chief, LMG, NIA

Others: Elizabeth M. Burke, Clinical Associate, LMG, NIA  
David B. Danner, Senior Staff Fellow, LMG, NIA  
Darryl Murrar, Biologist, LMG, NIA  
Samuel Yoon, Bio-Tech, LMG, NIA

## COOPERATING UNITS (if any)

Division of Dermatology, Boston Univ. School of  
Medicine (B. Gilchrest and M. Yaar)  
Dept. of Geriatrics, Johns Hopkins School of Medicine (W. B.  
~~Greenough and R. B. Bennett~~)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS

.95

## PROFESSIONAL

.95

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
    — (a1) Minors  
    — (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It is the purpose of this study to adapt the methodology used to measure the levels of specific mRNAs in biopsies of human skin, particularly from chronic wounds. Specifically the polymerase chain reaction is being utilized to measure mRNA levels for collagenase and for collagen. Also the levels of these mRNAs are being assayed in fibroblasts cultured from skin biopsies of individuals of varying age to identify possible alterations in gene regulation.



LPC-IRP-NIA

LN-IRP-NIA



ANNUAL REPORT OF THE LABORATORY OF NEUROSCIENCES  
NATIONAL INSTITUTE ON AGING  
1989-1990

I. ORGANIZATION AND MISSION STATEMENTS:

The Laboratory of Neurosciences (LN) at the National Institute on Aging was formed in 1978, and is involved in research on the central and peripheral nervous systems in health, aging and disease, including Alzheimer's disease. The Laboratory is located at the Clinical Center in Bethesda, Maryland, and is divided into three sections entitled, (1) Cerebral Physiology and Metabolism, (2) Brain Aging and Dementia, and (3) Neurochemistry and Brain Transport. In addition, there are four Units which were formed in 1987 and 1988, entitled (1) Positron Emission Tomography, (2) Neuropsychology, (3) Pharmacology and Pharmacokinetics, and (4) Brain Imaging and Computers. In September 1982, a six-bed temporary Patient Care Unit (PCU) was established to study inpatients with Alzheimer's disease and other dementias, as well as healthy subjects. The PCU, moved to permanent quarters on the 6D Ward in 1990. An Outpatient Clinic also was started in 1982 to screen subjects of inpatient protocols and to carry on outpatient-related research.

A. REPORT ON SECTION ON CEREBRAL PHYSIOLOGY AND METABOLISM (STANLEY I. RAPOPORT, CHIEF)

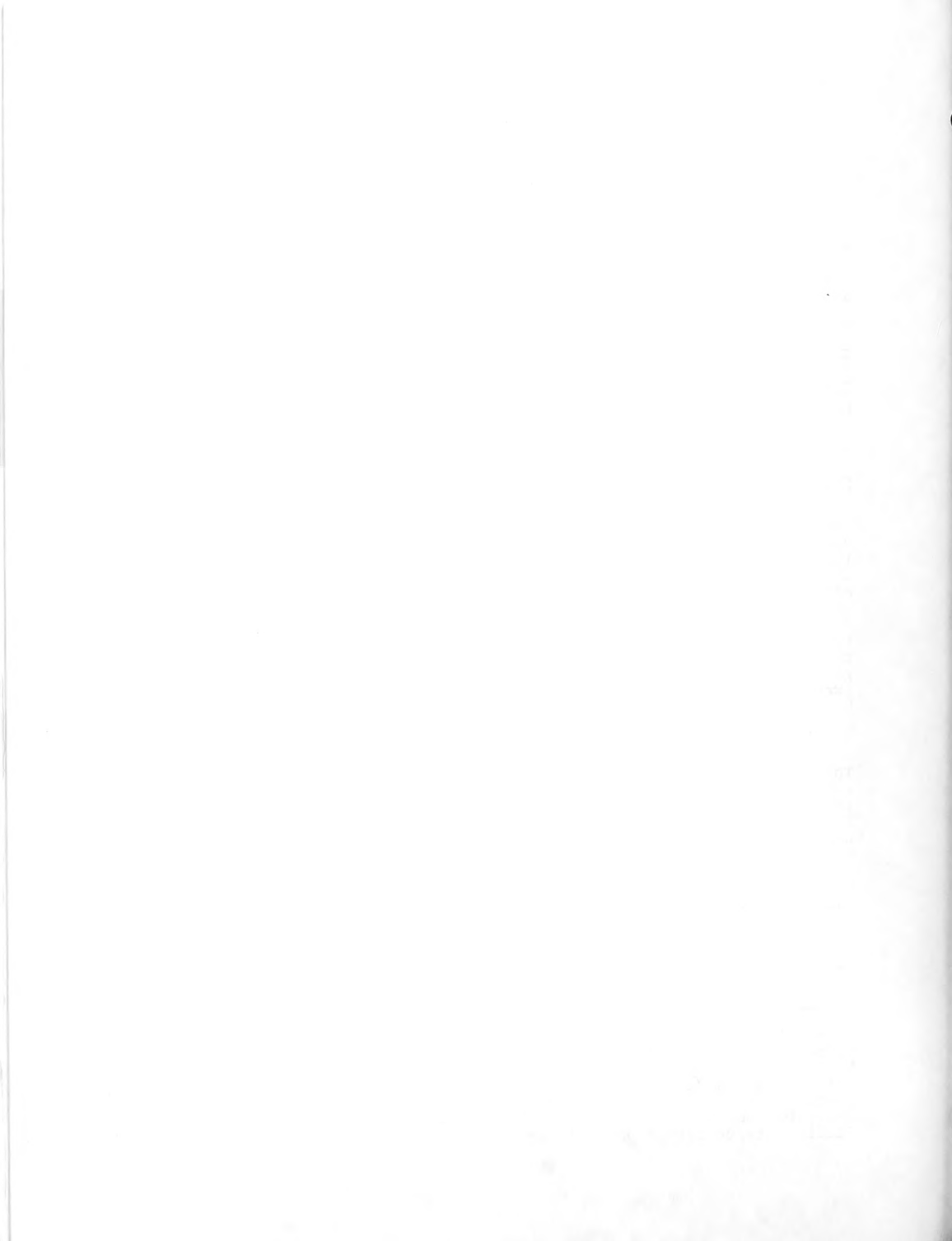
This section investigates the function, structure, physiology, biochemistry, and pharmacology of the central and peripheral nervous systems and the changes that take place during development and aging. Areas of investigation include the application of in vivo techniques to study brain glucose and lipid metabolism (using radioactive 2-deoxy-D-glucose or fatty acids); examination of the structure and function of the blood-brain and blood-nerve barriers, in disease models and before and following modification, in relation to chemotherapy of central nervous system disease; the use of tissue culture techniques to examine neuronal electrical properties in relation to altered genetic composition (trisomy 16 mice); the use of histological techniques to examine neuronal morphology and plasticity; neurochemical and molecular biological techniques to examine the Alzheimer brain.

B. REPORT ON SECTION ON BRAIN AGING AND DEMENTIA (MARK B. SCHAPIRO, CHIEF)

This section examines the metabolic, anatomic, neurochemical and neuropsychological parameters that characterize cerebral function in the following subject groups, so as to understand aging and disease of the brain and to provide a differential diagnosis of Alzheimer's disease and other dementias: (1) healthy men and women at different ages; (2) treated chronic hypertensives, (3) dementia of the Alzheimer type, (4) multiple infarct dementia, (5) Down syndrome, (6) depression in the elderly. The section employs positron emission tomography to examine cerebral metabolic rates for glucose and cerebral blood flow, computerized CT and magnetic resonance imaging to evaluate brain anatomy, analytical techniques to explore the composition of cerebrospinal fluid, and neuropsychological tests to evaluate the details of cognitive function. The program has initial cross-sectional studies followed by longitudinal studies with post-mortem followup.

C. REPORT ON UNIT OF POSITRON EMISSION TOMOGRAPHY (CHERYL L. GRADY, CHIEF).

This Unit is responsible for conducting research involving positron emission tomography on human subjects in relation to development abnormalities of the brain, including retardation; aging; and dementia, including Alzheimer's disease and multiple infarct dementia (see Section heading). Clinical protocols are formulated to examine brain glucose utilization using 18-F-2-deoxy-D-glucose; and blood flow using 15O-water, as positron-emitting tracers. Studies are performed on subjects at rest, with reduced visual and auditory



inputs; to obtain baseline measures of cerebral metabolism; and in repeated fashion with well-defined cognitive or physiological stimulus paradigms to determine patterns of activation during different task conditions. Metabolic data are related to data obtained with CT and neuropsychological measures.

D. REPORT ON UNIT ON NEUROPSYCHOLOGY (JAMES V. HAXBY, CHIEF).

This Unit is responsible for the design, implementation and analysis of neuropsychological research on memory, language, cognition and attention in healthy subjects and in patient groups noted above. A goal is to identify and describe changes in mental abilities that are a function of age or age-related disease, to propose and test cognitive models for these changes, and to relate them to neuroanatomic, neurochemical and physiologic changes that are concurrently measured. The Unit participates in clinical protocols to evaluate cognitive and behavioral effects of centrally acting drugs, including possible therapeutic agents for the treatment of Alzheimer's disease.

E. REPORT ON UNIT OF PHARMACOLOGY AND PHARMACOKINETICS (TIMOTHY SONCRANT, CHIEF).

This unit is responsible for conducting research on the sites and modes of action of centrally acting drugs, in animals and humans, in relation to peripheral pharmacokinetics, behavioral and cognitive responses and metabolic changes within the brain. Animals are examined using behavioral testing and quantitative autoradiographic procedures with various isotopes to localize central drug action. Humans are studied in relation to age and neurodegenerative disorders, including Alzheimer's disease, depression, and extrapyramidal signs. Drugs are evaluated for therapeutic efficacy, using cognitive and other measures. Cerebrospinal fluid concentrations of neurotransmitters and their metabolites are measured by analytical techniques, often developed by the Unit. The Unit also trains clinicians in the proper conduct of research in clinical pharmacology and therapeutics.

F. REPORT ON SECTION ON NEUROCHEMISTRY AND BRAIN TRANSPORT (QUENTIN R. SMITH, CHIEF).

The function of this section is to conduct research on the transport, distribution, metabolism, and physiological actions of critical substances within the central and peripheral nervous systems in relation to brain function, aging and disease. The program examines the cerebral uptake, distribution and actions of environmental toxins, such as heavy metals which may have a key role in brain aging and dementia. In addition, the program explores the mechanisms that regulate cerebral metabolism, protect the brain from circulating toxins, and maintain a stable ionic environment for neuronal function.

G. REPORT ON UNIT ON BRAIN IMAGING AND COMPUTERS (BARRY HORWITZ, CHIEF)

This unit is responsible for conducting research involving in vivo structural imaging of the human brain in healthy subjects and in the patient groups noted above. Images are obtained using x-ray computer-assisted tomography (CT) and magnetic resonance imaging (MRI). Quantitative volumetric analyses are performed in order to assess differences in volumes of significant brain structures (e.g., ventricles, basal ganglia), and to determine volumetric changes in individuals followed longitudinally. This unit also conducts research on human in vivo brain phosphorus metabolism using magnetic resonance spectroscopy (MRS). In addition, this unit conducts research involving the use of multivariate statistical methods and computer computational techniques for analyzing functional activity as measured by PET.





## II. RESEARCH HIGHLIGHTS

This section summarizes selected research accomplishments from the Office of the Chief (Stanley I. Rapoport) and Section on Cerebral Physiology and Metabolism, not summarized under later Section or Unit Headings.

### A. BRAIN FUNCTION IN AGING AND DEMENTIA.

1. Phylogenetic hypothesis for Alzheimer's disease. PET demonstrates selective metabolic involvement of the frontal, parietal and temporal association neocortices in Alzheimer patients, and lack of involvement of primary and sensory motor regions. Furthermore, Alzheimer neurofibrillary tangles are selective to the association as compared to primary sensory and motor cortical regions, and Alzheimer neuropathology is found in nonneocortical brain regions which underwent rapid changes during recent hominid and higher primate evolution. Because of these and other observations, it is suggested that Alzheimer's disease is a phylogenetic disease which involves brain regions which underwent rapid expansion during evolution of higher primates. This work was done by S. Rapoport.

### B. FUNCTIONAL INTERACTIONS BETWEEN BRAIN REGIONS

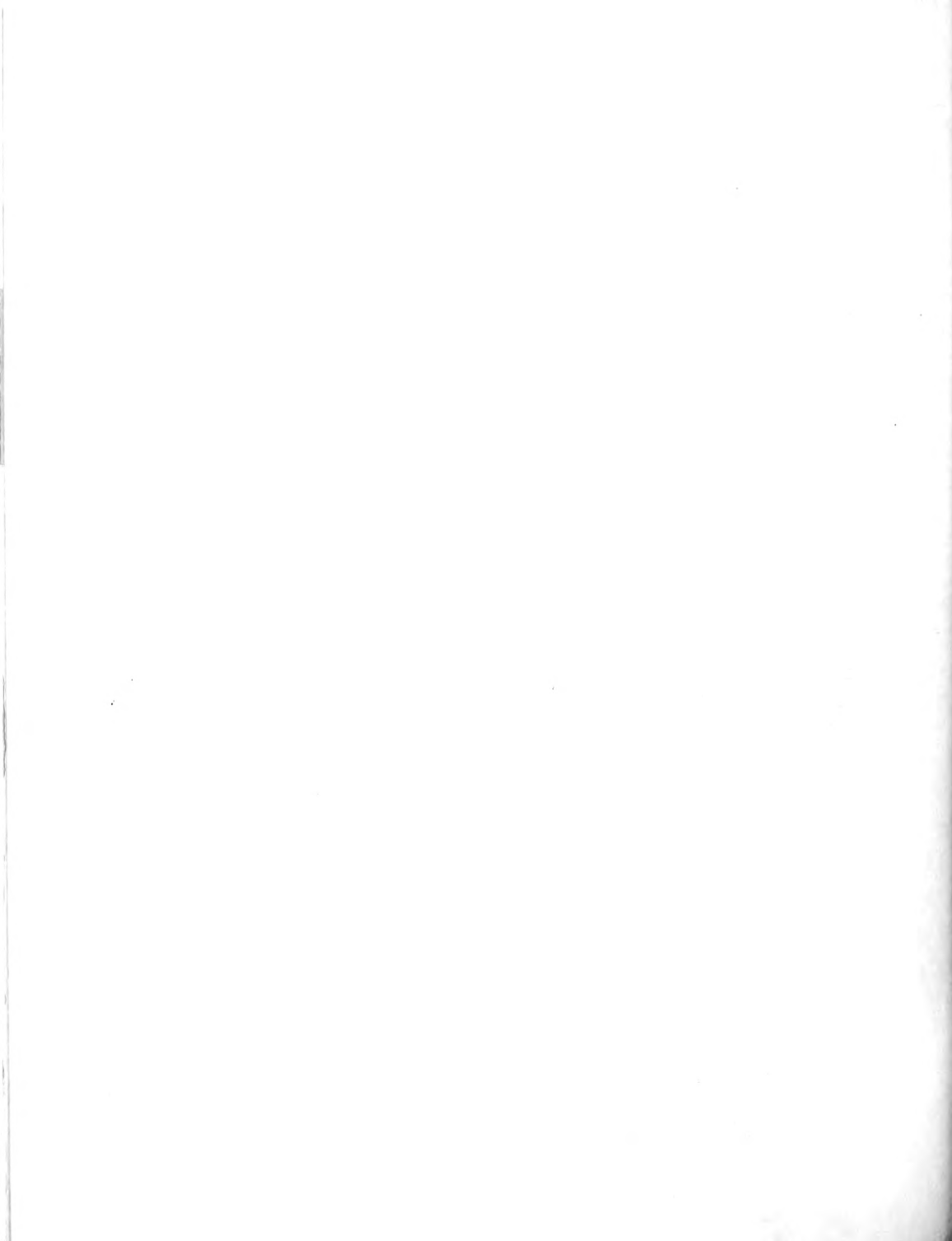
1. Application of correlation matrix to clinical subject groups. The correlation matrix approach to PET-derived cerebral metabolic rates was related to assumptions that the brain is composed of networks of neuronal units whose integrated activities subserve cognition and behavior. Its application to different subject groups was evaluated. Matrix analysis suggests that functional interactions between ipsilateral parietal and frontal association areas are reduced in the elderly, consistent with reduced "fluid" intelligence and visuospatial ability; that cortical-cortical and noncortical-cortical interrelations are altered in autism, consistent with altered directed attention; and that Broca's area is functionally disconnected in young adults with Down syndrome, as are thalamic regions, consistent with language problems and increased distractibility in these subjects. In view of studies following corpus callosotomy in rats, reductions of both interhemispheric and intrahemispheric correlations within the Alzheimer brain are consistent with a primary defect of pyramidal association neurons which contribute to both sets of correlations. Hypotheses concerning network abnormalities, derived from resting matrix data, have to be tested in subjects performing tasks proposed to be mediated by those networks. This work was done by S. Rapoport and B. Horwitz.

### C. BRAIN ANATOMY IN AGING AND DEMENTIA.

1. White Matter Hyperintensities in Chronic Treated Hypertension. T2-weighted magnetic resonance images (MRI), obtained on subjects with well-controlled hypertension who were neurologically normally and otherwise asymptomatic, demonstrated Grade 3+ white matter hyperintensities in 2 of 10 cases, and multiple small white matter hyperintensities in several more. Minimal changes were found in age matched, normotensive controls. Brain metabolism was abnormal clearly in the 2 cases with Grade 3+ MRI changes. These results suggest that MRI can be used to identify hypertensive subjects with possible premorbid evidence of brain disease. Longitudinal studies are being conducted to determine whether disease symptoms will appear in asymptomatic subjects with MRI abnormalities. This work was done by J. Salerno.

### D. CEREBROSPINAL FLUID CHEMISTRY IN AGING AND DEMENTIA.

1. CSF Production in Healthy Aging. The rate of CSF production, measured using a draining method from lumbar CSF, was reduced by half in older as compared with younger healthy subjects, from 0.4 to 0.2 ml/min.



Rostrocaudal gradients of protein did not differ between the groups. As CSF spaces are larger in the elderly, a lower production rate indicates that turnover of CSF, which acts as a sink for washout of brain substances, is reduced by more than half in the elderly. This work was one by C. May.

2. CSF Polyols in Aging and Disease. Measurement of polyols, reduction products of monosaccharides, may be useful for examining brain carbohydrate metabolism in vivo. A method was developed to make such measurements, using gas chromatography with flame ionization detection. In healthy controls, concentrations of erythritol, arabitol, ribitol and myoinositol were greater in CSF than in plasma, indicating a central nervous system source for these polyols. CSF concentrations of erythritol and myoinositol (normalized to plasma concentrations) were found to rise with age; Alzheimer patients had higher concentrations of CSF erythritol. These studies suggest a new approach to examine brain carbohydrate metabolism in aging and disease. The work was done by S. Rapoport.

#### E. BRAIN LIPID METABOLISM, RELATION TO FUNCTION AND AGING.

1. Mathematical model for brain incorporation of plasma palmitate. A three compartment mathematical model was developed by P. Robinson and S. Rapoport to interpret and calculate, from experimental data, the rate of palmitate uptake by brain from plasma, J<sub>palm</sub>. The model includes entry of palmitate from plasma into brain, de novo synthesis from acetate, and turnover of palmitate-containing brain lipids. It can be used to determine values of transfer constants between brain and blood, and to interpret time-dependent changes in brain radioactivity following the i.v. injection of a radiolabeled fatty acid.

2. Incorporation of [9,10-3H]palmitate into metabolic compartments of the brain. It was shown that this tritiated palmitate has advantages over [14C]palmitate for studying brain structure and function, because the tritiated tracer provides higher resolution autoradiographs, and because the products of its beta-oxidation, mainly 3H<sub>2</sub>O, are removed during drying for autoradiography. Following intravenous injection, this tracer is incorporated (within 15 min) mainly within brain phospholipids, particularly phosphatidyl choline, and thus can be used to mark turnover or synthesis of this phospholipid in vivo. This work was done by J. G. Noronha and colleagues.

3. Incorporation of [1-14C]arachidonate into brain phospholipids. Arachidonic acid, a C20 polyunsaturated essential fatty acid, is derived from dietary sources and is a major component of brain phosphoinositides. Following intravenous injection in rats, it is taken up by brain regions near maximally by 5 min, and is a marker particularly of phosphatidyl inositol. As such, it can be used to examine in vivo turnover and synthesis of this phospholipid. This work was done by J. DeGeorge and colleagues.

4. Fatty acid incorporation into brain following cholinergic stimulation. Arecoline, an M1 muscarinic agonist, when given to awake rats caused a 30% increase in [1-14C]arachidonate incorporation into brain, but did not alter [9,10-3H]palmitate incorporation. Increased arachidonate incorporation was blocked by atropine, a muscarinic receptor antagonist, and occurred in association with the distribution of M1 cholinergic receptors. Thus, [1-14C]arachidonate can be used to examine neurotransmitter-receptor coupling in vivo for transmitters using the phosphoinositide second messenger system. This work was done by J. DeGeorge and colleagues.

#### F. MOLECULAR BIOLOGY OF BRAIN AGING AND DISEASE.

1. pp60c-src Protein Tyrosine Kinase Expression in Rat Brain in Relation to Age. The activity of the pp60c-src protein tyrosine kinase was measured and found not to vary in brains of rats aged 4, 14-16 and 22-23 months. The relative levels of the pp60c-src protein also did not differ with regard to age. These age invariances indicate that changes in tyrosine kinase do not



contribute to aberrant phosphorylation in the aging nervous system. This work was done by G. Yang.

2. Identification of HMG-14 Gene on Mouse Chromosome 16. The gene for human high-mobility-group (HMG) chromosomal protein HMG-14 is located in region 21q22.3 of human chromosome 21, a region associated with the pathogenesis of Down syndrome. RNA blot analysis and detailed analysis of HMG-14 protein levels indicated that mouse trisomy 16 embryos have approximately 1.5 times more HMG-14 mRNA and protein than their normal littermates, suggesting a gene dosage effect and demonstrating the presence of this gene on this mouse chromosome. The HMG-14 gene may be an additional marker for Down syndrome. Chromosomal protein HMG-14 is a nucleosomal binding protein that may confer distinct properties to the chromatin structure of transcriptionally active genes, and therefore may contribute to the etiology of Down syndrome. The work was done by M. Matocha, in collaboration with M. Bustin.

3. Hypertrophy of Paraganglia in Relation to Age. The increase in numbers of extra-adrenal chromaffin cells of abdominal paraganglia in senescent F344 rats was investigated by 5-bromo-2'-deoxyuridine autoradiography. The results indicated that hypertrophy of the paraganglia in aged F344 rats is not due to proliferation of extra-adrenal chromaffin cells. They suggest that the chromaffin cell phenotype is induced in pre-existing cells and that the glucocorticoid receptor has an intrinsic role in this change. This work was done by G. Yang.

#### G. BLOOD-BRAIN BARRIER AND CENTRAL NERVOUS SYSTEM FUNCTION.

1. Cerebrovascular permeability to lipophilic vinca alkaloids. The vinca alkaloids vincristine and vinblastine are important agents in the chemotherapy of cancer. In rats, despite their high lipophilicity, their cerebrovascular permeability was quite low, even after correcting for plasma protein binding. It is likely that their large size (mol wts exceed 900 daltons) allows physical separation of charged and noncharged regions within the molecule, and that this factor, as well as overall lipophilicity, is an important determinant of their blood-brain barrier permeability. This work was done by N. Greig and colleagues.

2. Chemical modification of water soluble drugs for enhancing brain uptake. The alkylating anticancer agent, chlorambucil, was made into a number of esters to increase its lipid solubility and brain uptake. The tertiary butyl ester of chlorambucil was found to have optimum properties, as its half-life in plasma was prolonged, it rapidly entered the brain as compared with chlorambucil, and it retained significant alkylating activity. Recently, this ester was shown to have significant activity against human tumors grown in vitro, and is entering into clinical testing. This work was conducted by N. Greig and colleagues.

3. Brain uptakes of anti-cancer, water-soluble drugs. The pharmacokinetics of melphalan and chlorambucil, two structurally related anticancer drugs, were described in rats. The brain uptake of chlorambucil was low, but that of melphalan was greater than expected from its lipid solubility, due to its facilitated transport by the large neutral amino acid carrier at the blood-brain barrier. Brain uptakes of both drugs were nevertheless insufficient for treatment of central nervous system tumors. For these drugs to be centrally effective, their uptake must be enhanced by chemical modification. This work was done by N. Greig.

4. Osmotic modification of blood-brain barrier for central nervous system chemotherapy. It was shown that inadequate delivery of essential chemotherapeutic drugs to the brain, due to an intact or partially intact blood-brain barrier, probably accounts for poor therapeutic responses of patients with brain tumors. Drug delivery in such patients can be enhanced by osmotic opening of the blood-brain barrier, following intracarotid infusion



of a concentrated mannitol solution. The procedure causes morbidity in less than 1% of cases, and significantly prolongs survival of patients with primary lymphoma or glioblastoma (Phase II studies). Phase III (controlled clinical trials) are now intended to evaluate the efficacy of the osmotic procedure. This work was done by S. Rapoport.

5. How Intracerebral Diffusion and Vascular Permeability Determine Drug Access to Brain Tumors. A mathematical model describing drug uptake into brain tumors, directly from blood and indirectly from neighboring tissue, was elaborated. The model describes the influence of osmotic opening of the blood-brain and blood-tumor barriers on enhancing drug entry and tumor chemotherapy. It provides a quantitative framework for optimization of the osmotic procedure, which currently is used clinically for treatment of primary brain lymphoma and glioblastoma. This work was done by S. Rapoport and P. Robinson.

6. Increasing Annual Incidence of Primary Malignant Brain Tumors in the Elderly. Data were obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program on age-specific brain tumor incidence and tumor classification. During 1973 and 1985, it was calculated that total age-adjusted incidence of primary malignant brain tumors in the United States, all races, men and women, rose by 10.7%. However, age-adjusted incidences in the elderly rose much more dramatically, by 90% in subjects 75-79 years, by 300% in subjects 80-84 years, and by 400% in subjects 85 years and older. The most common types of malignant brain tumors in the elderly were astrocytomas and glioblastomas. Two possible causes may account for this rise in incidence in the elderly: introduction and extensive use of computer assisted tomography (CT), or a true increase in incidence due to an environmental or other factor. An increase in mortality due to brain tumors in the elderly, during the same survey period, suggests that the latter factor is important. Clearly, malignant brain tumors have become a greater factor contributing to morbidity and death in the elderly, since 1973. This work was done by N. Greig.

#### H. REGULATION OF NEURONAL DEVELOPMENT.

1. Sodium action currents in cultured trisomy 21 neurons. Using voltage clamp procedures, two inward sodium currents were identified in trisomy 21 human dorsal root ganglion neurons in culture. The neurons had been replated to remove excessive dendrites and axonal connections and to reduce interference of membrane capacitance. These currents were: a slow, tetrodotoxin-insensitive current (accounting for 90% of net) and a fast tetrodotoxin-sensitive current (accounting for 10% of net). Deactivation kinetics of the slow component were significantly reduced in the trisomic as compared to control neurons. Furthermore, inactivation curves for both components had a 10 mV shift in the depolarizing direction in the trisomic neurons. The changes in kinetics and in the inactivation curve can account for acceleration of the depolarization of the action potential in trisomy 21 neurons. This work was done by P. Caviedes.

2. Membrane properties of neurons of trisomy 16 mice. Trisomy 16 in the mouse is a model for trisomy 21 (Down syndrome) in humans, as specific genes on murine chromosome 16 correspond to genes on human chromosome 21 which contribute to the Down phenotype. Experimental conditions were established to culture dorsal root ganglion and spinal cord neurons from fetal trisomy 16, trisomy 19 and control mice. Patch clamp electrodes were employed to measure electrical membrane properties. Trisomic neurons had a faster rate of rise of the action potential (depolarization), and a faster rate of fall of the action potential (repolarization), than control neurons, resulting in a shorter overall action potential. Overproduction of products of genes on chromosome 16 in the mouse results in abnormal electrical properties of neurons during development. Furthermore, the action potential abnormality in murine trisomy 16 neurons corresponds to the abnormality in human trisomy 21 neurons. It is absent in trisomy 19 mice, indicating its specificity. This





work was done by B. Ault.

3. Electrical properties of transgenic mice with extra copies of human Cu/Zn superoxide dismutase. The gene coding for Cu/Zn superoxide dismutase, which resides on the human 21st chromosome and murine 16th chromosome, when replicated in transgenic mice, did not produce the abnormal action potential noted with both the human and murine trisomies; thus, Cu/Zn superoxide dismutase does not play a role in the abnormal action potential phenotype. This work was done by B. Ault and colleagues.

4. Transplanted Trisomic Brain Tissue. Murine trisomy 16 (Tsl6) is a model for human trisomy 21 (Down syndrome), as many of the genes on murine chromosome 16 are also found on human chromosome 21. However, the mouse trisomic 16 fetus dies in utero, and long term pathological changes cannot be examined in this model. Brain transplants of Tsl6 mice to 6-12 graft hosts were made, and found to be successful with survival for up to 6 months. Littermate control brains also were successfully transplanted. The transplanted tissue may be a model for brain changes in Down syndrome as well as in Alzheimer's disease (which occurs in older Down subjects). These experiments were done by B. Ault.



Employee RecognitionAwards

Balbo, Andrea	Quality Step Increase
Bell, Jane	Performance Award
Daly, Eileen	Performance Award
Dennard, Faye	Performance Award
Holloway, Harold	Performance Award
Larson, Denise	Quality Step Increase
Segal, Anne Kogan	Quality Step Increase
Stoll, James	DNA
Tung, Joyce	Performance Award

Staff Accomplishments

Ault, Brian	Attended Society for Neurosciences Annual Meeting in October 1989.
Caviedes, Pablo	Attended Society for Neurosciences Annual Meeting in October 1989.
Chandrasekaran, Krish	Attended Society for Neurosciences Annual Meeting in October 1989.
Coan, Elizabeth	Attended Society for Neuroscience Annual Meeting, Oct/Nov 1989.
DeGeorge, Joseph	Attended Society for Neuroscience Annual Meeting, October 1989.
Freo, Ulderico	Attended Society for Neuroscience Annual Meeting, October 1989.
Genka, Shigeru	Attended Society for Neuroscience Annual Meeting, October 1989.
Greig, Nigel	Attended Society for Neuroscience Annual Meeting, October 1989.
Matocha, Martha	Attended Society for Neuroscience Annual Meeting, October 1989.
Nariai, Tadashi	Attended the 37th Annual Meeting of the Society of Nuclear Medicine. Presented a paper entitled "Brain tumor imaging by dl-Erythro 9, 10-[18F] palmitate in rats". Washington, D.C., June 19-22, 1990.
Soncrant, Tim	Attended the Annual Meeting of the Society for Neurosciences, October, 1989.
	Presented paper entitled "Rigorous evaluation of cholinergic enhancement therapy in Alzheimer's disease" at the Meeting of American College of Neuropsychopharmacology, Maui, Hawaii, 1989.
	Presented paper entitled "Improved autoradiographic resolution reveals substantial underestimation by the



Nariai, Tadashi	Neurochemistry	1/30-5/16/90	\$155
	Mathematical Biology	1/29-5/15/90	\$195
Purdon, David	Using Animals in Intramural Research: Guidelines for Investigators	4/5/90	\$75
Segal, Anne Kogan	Federal Supply Schedules Seminar	2/20/90	\$60
Tung, Joyce	Statistics for Biomedical Scientists	1/29/90-5/18/90	\$200
Wakabayashi, Shinichi	Using Animals in Intramural Research Guidelines for Investigators	9/20/90	\$75

### International Activities

Rapoport, Stanley

Participated in Symposium on "Imaging, Cerebral Topography and Alzheimer's Disease", Lille, France, October 15-19, 1989

Co-chaired a proposed session at the 28th Annual Meeting of the American College of Neuropsychopharmacology Symposium and presented an introductory lecture entitled, "Alzheimer's disease: A Phylogenetic Disease of Association Brain Regions", Maui, Hawaii, December 10-15, 1989.

Invited presentations entitled, "Positron Emission Tomography and Brain Metabolism in Aging and Alzheimer's Disease", and "A New Method to Examine Turnover of Brain Phospholipid in Vivo", London, England and Venice, Italy, April 2-10, 1990.

Participated in the 1st Toronto-Stockholm Symposium on the Nervous System and Fuel Homeostasis and presented invited address entitled, "Glucose Uncoupling in Brain Degenerative Disorders as Measured by PET". Toronto, Canada, June 26-30, 1990.

Participated in the Second International Conference on Alzheimer's Disease and Related Disorders. Presented a paper on "Neuroimaging/Brain Energy Metabolism". Toronto, Canada, July 15-20, 1990.

Participated as a chairman and discussant of session entitled "Emotions and Disease States", related to positron emission tomographic studies in humans. Copenhagen, Denmark, August 10-24, 1990.



iodoantipyrine method of blood flow in some regions of rat brain" at the Annual Meeting of the Society for Neuroscience, Phoenix, AZ, October, 1989.

Member, Advisory Group to Steering Committee and Executive Board, Building 10 Complex Infrastructure Modernization and Improvement Program.

Stoll, James

Attended Society for Neuroscience Annual Meeting in October 1989.

Williams, Wesley

Attended Society for Neurochemistry, Annual Meeting, Phoenix, AZ.

Attended FASEB Annual Meeting, Washington, D.C., April 1990.

### Training

Asthana, Sanjay	Using Animals in Intramural Research: Guidelines for Investigators	4/5/90	\$75
	Neurochemistry	1/30/90-5/15/90	\$158
Barton, Patricia	Basic Time and Attendance	3/1/90-3/2/90	\$125
	Introduction to NIH for New Support Staff	3/5/90-3/9/90	\$360
	Domestic Travel	3/26/90-3/30/90	\$210
	Foreign Travel	6/12/90-6/14/90	\$155
	DELPRO	6/25/90-6/29/90	\$325
Coan, Elizabeth	Computer Training Course	2/5/90-2/7/90	\$00
Daly, Eileen	Finnigan MAT Institute-ION Trap Detector Operations	4/23/90-4/27/90	\$1400
DeMicheli, Enrico	Using Animals in Intramural Research: Guidelines for Investigators	4/5/90	\$75
Dennard, Faye	Federal Supply Schedules Seminar	12/89	\$60
Hegedus, Lajos	Mass Spectrometry for Chromatographies	2/14/90	\$95
Larson, Denise	Federal Supply Schedules Seminar	2/20/90	\$60





RESEARCH ACCOMPLISHMENTS, AS REPORTED BY SECTION  
AND UNIT CHIEFS OF LABORATORY OF NEUROSCIENCES  
1989-1990

A. REPORT OF SECTION ON BRAIN AGING AND DEMENTIA (MARK B. SCHAPIRO, CHIEF).

This section examines the metabolic, anatomic, neurochemical and neuropsychological parameters that characterize cerebral function in the following subject groups, so as to understand aging and disease of the brain and to provide a differential diagnosis of Alzheimer's disease and other dementias: (1) healthy men and women at different ages; (2) treated chronic hypertensives, (3) dementia of the Alzheimer type, (4) multiple infarct dementia, (5) Down syndrome, (6) depression in the elderly. The section employs positron emission tomography to examine cerebral metabolic rates for glucose and cerebral blood flow, computerized CT and magnetic resonance imaging to evaluate brain anatomy, analytical techniques to explore the composition of cerebrospinal fluid, and neuropsychological tests to evaluate the details of cognitive function. The program has initial cross-sectional studies followed by longitudinal studies with post-mortem followup.

I. BRAIN ANATOMY IN AGING AND DEMENTIA.

1. Dementia in Down syndrome is associated with accelerated ventricular dilatation. Serial computer assisted tomography (CT) demonstrated progressive dilatation of the lateral ventricles in older down subjects who were demented, but not in older nondemented Down subjects or young adult nondemented Down subjects. As all Down syndrome subjects over 35 years have the senile (neuritic) plaques of Alzheimer's disease, but only a fraction have large numbers of neurofibrillary tangles (Wisniewski et al., 1986), these results suggest that dementia and accelerated loss of neurons occur in relation to neurofibrillary tangle accumulation in Down syndrome. Accelerated ventricular dilatation also occurs in Alzheimer's disease, where plaques and tangles are thought to appear concurrently. The results also show that accelerated ventricular dilatation is a marker for Alzheimer type degeneration. The work was done by M. Schapiro.

2. Dementia without retardation in partial mosaic trisomy 21. A 45-year-old woman with a mosaic partial translocation (duplication of q arm of chromosome 21) was shown to be demented but did not have a history of retardation (she had been a bank clerk). Metabolic and CT studies confirmed Alzheimer type changes. This study suggests that dementia and retardation exist at separate loci on chromosome 21, or that retardation may be dose related with regard to chromosome 21. This work was done by M. Schapiro.

II. NEUROLOGIC FUNCTION IN AGING AND DEMENTIA.

1. Basal metabolic rate in Down syndrome. The BMR was measured in Down syndrome subjects and controls using an open-circuit



indirect calorimeter. Absolute BMR, and BMR corrected for surface area or lean body mass did not differ between the two groups. These results suggest that systems controlling basal metabolism are not affected by extra genomic material from chromosome 21. This work was performed by M. Schapiro.

2. EEG alpha background and dementia in Down syndrome. Abnormal background EEG alpha activity in older demented Down subjects differentiated them from older Down subjects who were not demented. The subjects with decreased alpha backgrounds also had lower visuospatial skills, decreased attention span, larger cerebral ventricles and a global decrease in glucose utilization as compared to age-matched non-demented old Down subjects. The results provide a biological marker for Alzheimer type degeneration in Down syndrome, which is proposed to involve large numbers of neurofibrillary tangles and senile plaques, as well as accelerated cell death. This work was done by M. Schapiro.

B. REPORT OF UNIT ON POSITRON EMISSION TOMOGRAPHY (CHERYL L. GRADY, CHIEF)

This Unit is responsible for conducting research involving positron emission tomography on human subjects in relation to developmental abnormalities of the brain, including retardation; aging; and dementia; including Alzheimer's disease and multiple infarct dementia (see Section heading). Clinical protocols are formulated to examine brain glucose utilization using 18-F-2-deoxy-D-glucose; and blood flow using 150-water, as positron-emitting tracers. Studies are performed on subjects at rest, with reduced visual and auditory inputs; and in repeated fashion with well-defined cognitive or physiological stimulus paradigms. Metabolic data are related to data obtained with CT and neuropsychological measures.

1. Subtypes of dementia of the Alzheimer type (DAT). Metabolic heterogeneity was examined in 33 DAT patients using principal components analysis. Four subgroups of patients were identified. Group 1 (15 patients) showed the "typical" DAT metabolic pattern of deficits primarily in parietal and temporal brain regions, with relative sparing in frontal, primary cortical, and subcortical regions. Group 2 had 8 patients and was characterized by metabolic deficits in paralimbic cortical regions, including orbital frontal, anterior cingulate and insular cortex. Group 3 had 5 patients and a disproportionate left hemisphere metabolic abnormality that was seen in frontal, parietal, and temporal regions. Group 4 also had 5 patients and showed parietal deficits equivalent to those seen in Group 1, but also had frontal metabolic reductions. These results show that distinct AD subgroups can be identified on the basis of metabolic patterns. The subgroups also differed in performance on neuropsychological tests. This work was done by C. Grady.

2. Identical twins discordant for DAT. Three pairs of monozygotic twins, clinically discordant for DAT for between 7 and 10 years, were examined longitudinally. Affected twins showed decrease



cerebral glucose metabolism as measured with PET, as well as progressive ventricular dilatation as measured with quantitative CT, in comparison to age-matched controls. Unaffected twins showed no differences from controls either in CT or PET measurements. These data demonstrate discordance of DAT, confirmed by quantitative measures with PET and CT, indicate the importance of non-genetic factors in DAT. This work was conducted by A. Kumar and M. Schapiro.

3. High Resolution Scanning in Dementia of the Alzheimer type (DAT). We analyzed data from a group of patients with DAT collected on the Scanditronix and compared the data with earlier findings on the low-resolution ECAT II scanner. Forty-seven patients with DAT and 32 age-matched controls were scanned. rCMRglc values in most neocortical regions were significantly reduced in the DAT group compared to controls, even in mildly demented patients. In addition, the ratio of lobar to mean gray metabolic rate was reduced in the parietal lobe in all dementia groups, and in the temporal and frontal lobes in more severely affected patients. These results confirm our earlier findings of relative reductions in neocortical association regions, and extend them to include significant decreases in absolute metabolic rates. This work was conducted by A. Kumar, C. Grady and M. Schapiro.

4. Hypertension. A group of 8 hypertensive men who have been treated for hypertension for at least ten years were studied. Two of the 8 were found to have severe periventricular and deep white matter hyperintensities on T2-weighted magnetic resonance imaging (MRI) scans of the brain. These two also had significantly ( $p < 0.05$ ) greater numbers of hypometabolic regions of interest on PET, as compared to controls. On neuropsychological testing, all hypertensives had scores that did not significantly differ from those of controls. These findings suggest that severe white matter changes on MRI, in otherwise normal, treated hypertensives and in the absence of clinical findings, reflect subclinical brain disease. This work was done by J. Salerno, M. Schapiro and C. DeCarli.

5. Cerebrovascular Dementia. Ten patients with dementia and white matter changes on MRI (DWMC) were compared to 23 age and severity matched DAT patients and 46 healthy controls. Patients with DWMC had significantly increased prevalence of hypertension, focal neurologic signs and infarcts on CT or MRI. Mean global glucose metabolism as measured by PET was not different between the two demented groups. Ratios of regional to global metabolism were significantly lower in subcortical regions ( $1.23 \pm 0.13$  vs  $1.35 \pm 0.13$ ) and higher in parietal regions ( $0.91 \pm 0.14$  vs  $0.81 \pm 0.11$ ) in DWMC patients compared to those in DAT patients. We conclude that patients with DWMC have increased prevalence of cerebrovascular disease and show a different pattern of cerebral metabolic deficit than do patients with DAT. This work was done by C. DeCarli and C. Grady.

6. Cognitive Activation of Regional Cerebral Blood Flow (rCBF).



The presence and neuroanatomical location of separate visual pathways for processing spatial location and object identity were identified in 10 young (mean age  $27 \pm 5$  yrs) and 10 old subjects (mean age  $72 \pm 7$  yrs) using [150] water and PET. Double dissociations were demonstrated in both young and old subjects—i.e., the spatial location task selectively activated the superior parietal regions and the object recognition task preferentially activated the occipito-temporal regions. There was no difference in the magnitude of activation in these areas in the old subjects compared to the young subjects. Activation was also seen in some frontal brain regions but there was not a significant difference between the two tasks in these frontal areas. These results suggest that the dissociation of object and spatial vision in extrastriate cortex is maintained in the elderly. This work was done by C. Grady, J. Haxby, B. Horwitz and M. Schapiro.

7. Aging, Dementia and Down syndrome. We measured rCMRglc with PET in 15 young adult DS subjects aged 19-33 years, in 4 older (greater than 40 years) non-demented patients, and in 3 older demented patients. For both association and primary neocortex, nondemented old DS subjects had glucose metabolic values that were more similar to values in the young DS subjects. On the other hand, demented older DS subjects had significantly lower values of rCMRglc than both young and older non-demented DS subjects, with the greatest reductions in association neocortex. Thus, glucose metabolism is reduced significantly only in older DS subjects with clinical dementia. The specific involvement of parietal-temporal association neocortices is similar to dementia of the Alzheimer type in premorbidly normal subjects. This work was done by M. Schapiro and J. Haxby.

We studied 14 healthy, noninstitutionalized DS subjects (mean age 30 years, range 25-38) and 13 sex-matched, healthy volunteers (mean age 29.5 years, range 22-38). In the DS group, mean mental age on the Peabody Picture Vocabulary Test was 7.8 years. Resting global gray CMRglc equaled  $8.76 \pm 0.76$  (mean  $\pm$  SD) mg/100g/min in the Down Syndrome group as compared with  $8.74 \pm 1.19$  mg/100g/min in the control group ( $p < 0.05$ ). Gray matter regional measurements and ratios of rCMRglc to global CMRglc also did not differ between groups. These results show that healthy young Down syndrome adults do not have abnormal regional or global brain glucose utilization prior to the age at which the neuropathology of Alzheimer's disease is reported to occur. This work was done by M. Schapiro and C. Grady.

Regional cerebral blood flow (rCBF) of cortical gray matter, IS, also was measured with the noninvasive Xenon 133 inhalation method on 2 consecutive days in 11 healthy, noninstitutionalized subjects with trisomy 21 Down syndrome (DS) (mean age 28.0 years) and in 22 sex-matched healthy volunteers (mean 27.3 years). IS did not differ between groups for any lobar region. The ratio of rIS to hemispheric IS, right/left and frontal/nonfrontal ratios also failed to show significant regional differences between groups. These results show that healthy young DS adults do not show





abnormalities in rCBF, as measured with Xenon 133 clearance, prior to the age of 35 years. This work was done by M. Schapiro and K. Berman.

8. Aging and Brain Metabolism. Cerebral glucose metabolism was determined by positron emission tomography (PET), with 18F-2-deoxy-D-glucose (18FDG), in 60 healthy volunteers (23 men, 37 women) between the ages of 21 and 90 years. A new, high resolution PET scanner (Scanditronix) was employed. Whole brain metabolism declined significantly ( $p < 0.05$ ) by only 12% over a 70 yr period, indicating maintenance of functional brain integrity. The age effect on brain metabolism accounted for less than 10% of the variance. This work was done by C. Grady and M. Schapiro.

9. Brain Metabolism and Gender. No gender difference was noted in cerebral glucose metabolism in healthy adults, in contrast to previously reported studies with calculated rather transmission attenuation corrections in PET. This work was done by M. Schapiro, B. Horwitz and C. Grady.

10. Trichotillomania. We have examined glucose metabolism in trichotillomania (TM), a disease similar to Obsessive-Compulsive Disorder (OCD). Preliminary analyses show that global metabolism is significantly increased in the group of 10 adult female controls. In addition, several regions showed between group differences in mean glucose metabolic ratios, but none of these areas had been postulated to be involved in TM, based on our work with PET and OCD, and our hypothesis that TM might be part of a spectrum of obsessive-compulsive behaviors. However we did find a significant correlation between responses to clomipramine and metabolism in the orbitofrontal and anterior cingulate regions, as was found in the OCD patients. This work was conducted by M. Schapiro, C. Grady, and S. Swedo.

11. Comparison of 2 PET scanners for longitudinal studies of brain metabolism. Our research involves the longitudinal study of brain glucose utilization in relation to the time course of cognitive decline in patients with Alzheimer's disease. Five controls and five Alzheimer patients were scanned at the same sitting using two PET scanners, the ECAT II (ORTEC, Life Sciences), on which initial data had been obtained; and the Scanditronix PC1024, on which current and future data are to be obtained. Regional correction factors were determined to allow comparison of data with the two machines. This work was done by C. Grady.

#### UNIT GOALS

##### Pet Methodology

1. Resting studies with 18-fluoro-2-deoxy-D-glucose (FDG). FDG studies in the resting state, eyes patched and ears plugged, will be continued on the Scanditronix PET scanner. In normals, the contribution of brain atrophy to the relation of CMRglc and age will be explored, using correction factors for cortical atrophy and



ventricular dilatation derived from quantitative CT and MRI scanning. In the DAT group, previous studies using the low resolution ECAT II scanner were unable to adequately evaluate metabolism in the temporal lobe and hippocampus. With the higher resolution Scanditronix, these areas can be studied. In all our patient groups, previous studies were done with 18-fluoro-deoxy-D-glucose (FDG). The procedure will be continued for longitudinal questions and for pharmacological studies, and to examine new patients groups in order to evaluate the specificity of differences demonstrated in DAT and Down syndrome.

2. Double FDG method. Two serial FDG injections will be made, 30 min apart, to allow a subject to be studied in a resting and a stimulated state in the same scanning session, thus reducing the coefficient of variation associated with scans done on separate days in separate subjects. In the normal population, studies in resting and sensory stimulated states will allow us to determine if the relation of CMRglc and age is state dependent. This double FDG method also will allow us to examine pharmacologic stimulation of the brain.

3. O15 Water. Because of this isotope's short half-life, multiple studies can be performed on the same subject during one session to measure regional cerebral blood flow. Cognitive stimulation of two different visual processing pathways is now being explored in normal subjects and patients with dementia. Other paradigms later will be developed, such as a task to activate frontal lobe centers of attention.

4. Drug studies. Drug studies will use one of several methods, including the double FDG technique, receptor ligands, or radioactive drug isotopes. These studies will study the sites and modes of action of drugs within the central nervous system. Drugs chosen will reflect hypotheses under consideration in our studies of aging and DAT, such as neurochemical deficiency, neurotransmitter imbalance (dopaminergic-cholinergic), bipterin deficiency, or altered neuronal plasticity (nerve growth factor). Such PET studies will be accompanied by complimentary methods used in this lab, including neuropsychologic battery, psychiatric assessment, adaptive behavioral scales, motor studies, hormonal studies, and pharmacodynamic endpoints (peripheral pharmacokinetics, plasma and CSF markets, brain concentrations).

5. Receptor studies. Radiolabeled ligands will be used to examine receptor density of neurotransmitter systems under consideration by us, such as the dopaminergic system. Such studies will examine changes in receptor population in relation to age and disease. Further, such radiolabeled ligands will be used in drug studies, as outlined above.

C. REPORT OF UNIT ON NEUROPSYCHOLOGY (James V. Haxby, Chief).

This unit is responsible for the design, implementation, and analysis of neuropsychological research on memory, language,



cognition and attention in healthy subjects and in patient groups noted above. The goal of this research is to identify and describe changes in mental abilities that are a function of age or age-related disease, to propose and test cognitive models for these changes that are concurrently measured. The Unit participates in clinical protocols to evaluate cognitive and behavioral effect of centrally acting drugs, including possible therapeutic agents for the treatment of Alzheimer's disease.

1. Activation and localization of cortical visual pathways. Studies of regional cerebral blood flow, as measured with  $^{15}\text{O}$  and positron emission tomography (PET), during the performance of spatial and object vision tasks in healthy men, demonstrated two anatomically distinct and functionally specialized pathways, the locations of which were not absolutely predicted from studies in nonhuman primates. Young and old adults had rCBF increases with similar magnitudes and spatial distributions. The  $^{15}\text{O}$ PET method should allow studying the functional organization of the association neocortices in Alzheimer's disease may provide a challenge test of regional brain function for earlier detection of neocortical abnormalities. This work was done by J.V. Haxby, C.L. Grady, B. Horwitz, M.B. Schapiro, M. Mishkin, L. Ungerleider, P. Herscovitch and R. Carson.

2. Preservation of verbal but not visual memory in healthy aging. In 60 healthy men, language abilities and verbal memory were found not to decline with age. Visuospatial cognition and visual memory, on the other hand, demonstrated significant age declines. These results suggest that an age decline of verbal memory, when reported, is a result of disease, but that visuospatial cognition and memory are diminished in the healthy elderly. This work was done by E. Koss and J.V. Haxby.

3. Age-related differences in non-effortful perceptual operations. The attentions cost of encoding operations in two simple, visual perceptual matching tasks was greater in older than younger subjects. This perceptual encoding operation is automatic and not effortful in young subjects, suggesting that age-related cognitive differences are not restricted to effortful processes. This work was done by P. Nestor under the supervision of J.V. Haxby and R. Parasuraman.

4. Longitudinal course of neuropsychological impairment in DAT. Longitudinal study of patients with DAT for as long as five years has shown that there can be an initial plateau phase during which only memory is impaired, but decline on other neuropsychological functions is not observed. Afterwards, neuropsychological decline on nonmemory cognitive abilities is remarkably linear. The rate of decline varies markedly among patients, but the rate for an individual is quite constant. After memory impairment, the first neuropsychological functions to demonstrate significant deficits in patients with mild DAT are attention, planning and foresight, and abstract reasoning. Patterns of nonmemory neuropsychological



impairments tend to persist over time, despite worsening severity of overall dementia. For example, patients with disproportionate verbal impairment relative to visuospatial impairment tend to demonstrate the same neuropsychological discrepancy at follow-up. The well-behaved, linear decline of neuropsychological function may provide the basis for a more sensitive evaluation of the efficacy of drug therapy designed to show or halt the progression of Alzheimer's disease. This work was done by J.V. Haxby and C.L. Grady.

5. Metabolic and neuropsychological patterns are correlated in DAT. In patients with moderate Alzheimer's disease, the relative disproportion of language vis-a-vis visuospatial impairments was significantly correlated with right-left asymmetry of regional cerebral metabolic rates for glucose (rCMRGlc). Moreover, discrepancies between calculations or immediate visuospatial memory span, on the one hand, and attention or verbal fluency, on the other, correlated significantly with metabolic discrepancies between parietal and frontal association cortices. In mildly demented patients, metabolic patterns were not correlated with nonmemory neuropsychological patterns. These patients had no significant impairments of nonmemory language and visuospatial functions with significant abnormalities of neocortical metabolism. Follow-up studies demonstrated significant deterioration of nonmemory neuropsychological functions which correlated with right-left metabolic asymmetries. These findings confirm that neocortical metabolic changes precede the development of demonstrable neocortically mediated neuropsychological impairments in early DAT. It appears that the brain is capable of compensating for these early physiological changes to maintain premorbid neuropsychological function. This work was done by J.V. Haxby and C.L. Grady.

6. Selective attention in healthy aging and DAT. Cognitive studies of selective and shifting attention to visual features in compound stimuli identified two dissociable underlying processes, one driven by intention and the other requiring priming with practice. These cognitive studies may provide a theoretical basis for explorations of the impairment of complex selective attention in early Alzheimer's disease. In a separate study, patients with DAT were found to have impaired selective attention to spatial location, such that they were less efficient at responding to stimuli in unattended locations. This impairment was correlated with superior parietal lobule rCMRGlc, providing evidence for the neuroanatomical basis for this aspect of the attentional impairment in DAT. This work was done by J.V. Haxby in collaboration with R. Parasuraman and P. Greenwood of Catholic University.

7. Neuropsychological evaluation of adults with Down syndrome. Down syndrome subjects over 35 years of age, without clinical dementia, demonstrated significant neuropsychological abnormalities relative to young Down adults. Abilities to form new long-term memories and visuospatial construction were consistently diminished, whereas immediate memory span and language were not.





These neuropsychological deficits may be the early consequences of Alzheimer's disease neuropathology. Older Down syndrome adults with dementia had global neuropsychological deficits, suggesting a stage of disease progression that corresponds to severe dementia in premorbidly normal adults with dementia of the Alzheimer type. The more selective neuropsychological deficits in nondemented Down syndrome adults suggests a correspondence to early and intermediate dementia of the Alzheimer type. This work was done by J.V. Haxby and M.B. Schapiro.

8. Neocortical metabolic abnormalities precede nonmemory cognitive impairment in DAT. DAT patients with mild impairment had no significant impairments of nonmemory language and visuospatial functions with significant abnormalities of neocortical metabolism. Follow-up studies demonstrated significant deterioration of nonmemory neuropsychological functions, which correlated with right-left metabolic asymmetries. These findings confirm that neocortical metabolic changes precede the development of demonstrable neocortically-mediated neuropsychological impairments in early DAT. It appears that the brain is capable of compensating for these early physiological changes to maintain premorbid neuropsychological function. This work was directed by J.V. Haxby and C.L. Haxby.

#### D. REPORT ON UNIT ON BRAIN IMAGING AND COMPUTERS (BARRY HORWITZ, CHIEF)

This unit is responsible for conducting research involving in vivo structural imaging of the human brain in healthy subjects and in the patient groups noted above. Images are obtained using x-ray computer-assisted tomography (CT) and magnetic resonance imaging (MRI). Quantitative volumetric analyses are performed in order to assess differences in volumes of significant brain structures (e.g., ventricles, basal ganglia), and to determine volumetric changes in individuals followed longitudinally. This Unit also conducts research on human in vivo brain phosphorus metabolism using magnetic resonance spectroscopy (MRS). In addition, this Unit conducts research involving the use of multivariate statistical methods and computer computational techniques for analyzing functional activity as measured by PET.

1. Quantitative CT analyses in healthy aging in men and women. The relation between age and gender and ventricular volumes were determined for 64 healthy men and 43 healthy women. Gender differences in ventricular volume were found (women having smaller left and right lateral ventricles than men), as was increased ventricular size with advancing age. Decline in cognitive processes (measured by the WAIS) and increased ventricular volume seem to be relatively independent processes correlated more to the age of the subject. This work was conducted by J. Kaye and C. DeCarli.

2. Identical twins discordant for DAT. Three pairs of monozygotic twins, clinically discordant for DAT between 7 and 10 years, were

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found using CT to have ventricular volumes significantly larger in the twin with DAT than in matched controls, although the unaffected twin was within normal limits. Rates of ventricular dilatation of each affected twin, determined by longitudinal CT scans, were more than 2 standard deviations larger than in controls. This work was conducted by A. Kumar.

3. Brain atrophy in AIDS dementia in children, with and without AZT treatment. Eight children (age range 2-24 years) with human immunodeficiency virus-induced encephalopathy were treated with chronic infusion of azidothymidine for 6 months. Intelligence quotients improved in 7 children who were tested, and dilatation of the lateral ventricles decreased. Thus, AZT can partially reverse or retard AIDS-related brain disease in children. This work was conducted by C. DeCarli and colleagues.

4. Magnetic resonance imaging and temporal lobe volumes in healthy aging. Coronal MRI images were used to determine temporal lobe volumes in healthy control subjects. Volumes of temporal lobes were found to correlate negatively with age. This research was performed by C. DeCarli and B. Horwitz.

5. White matter hyperintensities on MRI images. The prevalence of white matter hyperintensities identified on T2-weighted axial MRI images was found to increase slightly with healthy aging in subjects for whom cerebrovascular risk factors are absent. The presence of DAT does not increase the prevalence or severity of white matter hyperintensities above that seen in age-matched controls. Within the healthy elderly, the severity of white matter hyperintensities was correlated with age and systolic blood pressure, suggesting that higher systolic blood pressures, even when in the normal range, may be associated with increased prevalence of cerebrovascular disease. This work was performed by W. Kozachuk, C. DeCarli and B. Horwitz.

6. Brain metabolic patterns in Down syndrome. Pairwise correlations between rCMRglc, as determined by PET, were evaluated in 14 young adult Down syndrome (DS) patients and in 24 healthy age-matched controls. The DS group had many correlations within and between frontal lobe and parietal lobe regions with lower values than did the control group, with Broca's region being particularly affected. These results indicate a disruption of functional associations in the neocortex of DS subjects. This work was conducted by B. Horwitz and M. Schapiro.

7. Computer simulation model for correlational analysis. A computer simulation model was devised in order to provide a partial validation for correlation analysis as applied to metabolic data. Because the underlying pattern of functional couplings in the model is specified, these simulations demonstrate that the change in the correlation coefficient between normalized metabolic rates reflects the change in the corresponding functional coupling, and that correlational analysis provides more information on regional involvement in neural systems than does a region-by-region analysis



of metabolic rates. This work was carried out by B. Horwitz.

8. Functional coupling during visual processing. Correlational analysis was performed on normalized rCBF values, obtained by PET with [15-O]-labeled water, to examine functional interactions among brain regions in posterior neocortex in young men during two 2-choice, match-to-sample visual tasks: face discrimination (FD), and dot localization with rotation (DL). Although both tasks activated lateral occipital and occipitotemporal cortex bilaterally, correlational analysis revealed that during FD, occipital and occipitotemporal activations correlated significantly, but only in the right hemisphere. During DL, occipital and superior parietal activations correlated significantly, but again, only in the right hemisphere. These results support the view that FD and DL processing are carried out to a greater degree by the right posterior hemisphere. This work was performed by B. Horwitz, J. Haxby, C. Grady, and M. Schapiro.

E. REPORT ON UNIT ON PHARMACOLOGY AND PHARMACOKINETICS (TIMOTHY T. SONCRANT, CHIEF)

This report summarizes the two major projects within this Unit.

I. CLINICAL PHARMACOKINETICS, PHARMACODYNAMICS AND THERAPEUTICS

1. Biopterin in Alzheimer's disease. Biopterin was administered parenterally to subjects with probable Alzheimer's disease and low cerebrospinal fluid homovanillic acid concentrations. Cerebrospinal fluid biopterin levels were increased five-fold, and the homovanillic acid concentration was increased in 3 of 5 subjects. The results suggest a correctable brain biopterin deficiency that, in some subjects with Alzheimer's disease, may result in reduced dopamine turnover.

2. Age-related cognitive and psychomotor responses to haloperidol. Five young and five elderly subjects received haloperidol intravenously. Young subjects showed greater akathisia and sedation, and had higher plasma prolactin levels after haloperidol administration. The results suggest a reduced effect of brain dopamine receptor blockade on cognitive and motor function in aged humans. This work was conducted by P. Morris.

3. Dopamine turnover in the aged human brain. Eight young and four aged subjects received oral doses of debrisoquin, an inhibitor of the degradation of dopamine to homovanillic acid in the peripheral nervous system. Measured urinary excretion of homovanillic acid production, which then reflected brain dopamine turnover, was lower in elderly compared to young subjects. This finding suggests that dopamine turnover is reduced in the brains of healthy aged humans.

4. Arecoline pharmacokinetics in human subjects with Alzheimer's disease. Arecoline was administered intravenously to 12 demented elderly subjects, and plasma pharmacokinetics were measured. After



termination of the infusion, arecoline was cleared from plasma with a half-life of less than three minutes. Thus, arecoline is an ideal drug for a therapeutic trial in Alzheimer's disease because during continuous infusion, steady state drug levels can be rapidly achieved. This work was conducted by P. Morris and H.U. Shetty.

## II. CEREBRAL METABOLISM, RELATION TO BRAIN FUNCTION AND AGING

1. Cerebral glucose utilization during development. rCMRglc was measured in male Fischer-344 rats aged 7 to 90 days. Whole brain glucose utilization rose eight-fold between 7 and 45 days, then declined by 23% at 90 days. Prior to 30 days of age, rCMRglc in several forebrain regions, including neocortex, was lower, relative to whole brain values, than in adult rats, but by 30 days, the adult pattern was achieved. These results demonstrate large increases in brain glucose utilization during the first 45 days of life in rats, and suggest that maturation of the neocortex is delayed in comparison to other brain regions. This work was conducted by T. Soncrant.

2. Cholinergic function and age. Male Fischer-344 rats, aged 3 or 24 months, were administered arecoline and rCMRglc was measured. Cerebral metabolic responses did not differ significantly between the two age groups, indicating that muscarinic receptor and post-receptor mechanisms are intact in the senescent rat brain. This work was conducted by T. Soncrant.

3. Dopaminergic function and age. Peak metabolic and behavioral effects of haloperidol were significantly smaller in 33 month old than in 3 month and 12 month old Fischer-344 rats, despite higher brain concentrations of haloperidol in older rats that were due to slower drug elimination. Likewise, metabolic and behavioral responses to bromocriptine were reduced in 30 month, compared to 3 month old, male Fischer-344 rats. These age differences are consistent with reduced brain dopaminergic markers in old rats, and suggest an imbalance between dopaminergic and cholinergic activity. This work was conducted by G. Pizzolato and G. Ricchieri.

4. Serotonin system and age. Male Fischer-344 rats aged 3, 12, or 24 months were administered methiothepin and rCMRglc was measured. The metabolic response was smaller and anatomically more restricted in older rats. After the administration of m-chlorophenylpiperazine, metabolic responses were reduced, but not delayed, in 12 month and further reduced in 24 month, compared to 3 month old, rats despite the achievement of higher brain drug concentrations in the older animals. These results indicate presynaptic functional decrements in rat brain serotonergic systems during aging. This work was conducted by U. Freo and G. Ricchieri.

5. Nicotine effects on brain metabolism. In rats, nicotine stimulates brain metabolism in subcortical regions that contain high concentrations of nicotine receptors, but does not alter glucose utilization in neocortical regions possessing nicotine receptors. These results indicate that nicotinic cholinergic

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receptors in cortex function differently than do those in other areas, and that their loss in Alzheimer's disease may be without functional consequence. This work was conducted by T. Soncrant and D. McNamara.

6. Animal models of aging and disease. A model of neocortical cholinergic deficiency was developed by neurochemical ablation of neurons of the basal forebrain. Using parachloroamphetamine, a model of serotonin dysfunction was produced in young rats in which responses were altered in the same manner as they are in intact aged rats. These models will be useful in the study of age and disease effects on brain function and of neural plasticity. This work was conducted by Y. Lamour, U. Freo and E. De Micheli.

F. REPORT OF SECTION ON NEUROCHEMISTRY AND BRAIN TRANSPORT  
(QUENTIN R. SMITH, CHIEF)

The function of this section is to conduct research on the transport, distribution, metabolism, and physiological actions of critical solutes within the central and peripheral nervous systems in relation to brain function, aging and dementia. The program examines the cerebral uptake, distribution and actions of environmental toxins and metals which may have a role in brain aging and dementia. In addition, the program explores the mechanisms that regulate cerebral metabolism, protect the brain from circulating toxins, and maintain a stable ionic environment for neuronal function.

I. BRAIN NUTRIENTS AND METALS IN AGING AND DISEASE

1. Brain aluminum and silicon in Alzheimer's disease. H. Mori, C. Swyt (BEIB, NIH) and Q. Smith developed a quantitative, x-ray microanalysis method to determine regional brain levels of metals in unfixed, unstained, fresh-frozen human brain tissue. Analysis of brains from four patients with Alzheimer's disease demonstrated that neither aluminum nor silicon is accumulated in senile plaque cores or rims, as compared to surrounding brain tissue. Measured values for brain aluminum and silicon were similar to values for normal aged controls. The results suggest that aluminosilicates do not play a key role in senile plaque formation in Alzheimer's disease.

2. Transfer rates for selected metals at the blood-brain barrier. Metals have been implicated as potential environmental toxins in the pathogenesis of several neurodegenerative diseases. Yet, little is known about how metals are taken up into brain or what controls their rates of entry. V. Murphy determined blood-to-brain transfer coefficients for several selected metals in unanesthetized rats using an intravenous administration procedure. Values differed among metals by 100 fold with lead >> calcium = cadmium >> gallium (a metal similar to aluminum). The results indicate that metals differ widely in their ability to cross the blood-brain barrier and gain access to brain tissue.



3. Regulated transport of calcium at the blood-brain barrier. Calcium transport mechanisms have been found to facilitate the uptake of toxic metals in peripheral tissues. To determine if a calcium transport mechanism is present at the blood-brain barrier, V. Murphy varied plasma ionized calcium concentration in rats over a approximately 20-fold range by infusing sodium citrate or calcium chloride into the femoral vein. Calcium uptake rates into brain and cerebrospinal fluid were then quantitated using calcium-45. The  $^{45}\text{Ca}$  transfer rate into cerebrospinal fluid was found to be inversely related to plasma ionized calcium concentration, suggestive of the presence of a saturable transport system for calcium at the blood-CSF barrier. This transport system may also facilitate the uptake of other metals, such as lead and aluminum, into the central nervous system.

4. Nutrient transport mechanisms at the blood-brain barrier. An in vivo brain perfusion technique was developed to characterize blood-brain barrier transport systems for essential nutrients. Glucose, the primary substrate for brain oxidative metabolism, was shown to be transported across the blood-brain barrier by a single, low-affinity mechanism that operates normally half-maximal capacity. In contrast, neutral amino acids were found to be taken up into brain by a high affinity mechanism that is saturated with amino acids at normal plasma concentrations. The results provide transport constants and models that allow estimation of nutrient influx rates into brain under differing physiologic and pathologic conditions. This work was done by Q. Smith and colleagues.

5. Amino acid uptake during development and aging. T. Nagashima and Q. Smith demonstrated that neutral amino acid influx into brain decreases by 50% between 1 week and 3 months of age in the Fischer-344 rat. The reduction in influx was shown to be due to a decline in the transport capacity of the cerebrovascular large neutral amino acid carrier (the L system) and the disappearance of a second carrier that preferred small neutral amino acids (the A system). Between 3 months and 24 months of age, neutral amino acid transport into brain was found to be age invariant. The results demonstrate that neutral amino acid transport into brain declines during development, but is maintained during aging in the rat. The developmental changes in transport correlate well with reported changes in brain protein synthesis, consistent with the hypothesis that transport is modulated to meet the needs of brain metabolism.

## II. FUNCTION AND STRUCTURE OF PERIPHERAL NERVE

1. Blood-nerve barrier integrity during Wallerian degeneration. Frog sciatic nerve was transected close to the spinal cord, and then the integrity of the blood-nerve barrier was examined in the distal segment, from 1 week to 9 months thereafter. Endoneurial capillary permeability increased within one week after transection, reached a maximum by 2 weeks and then returned to normal by 6 weeks. The permeability of the perineurial sheath increased as well, but did not return to normal even after nine months following transection. The results suggest that the perineurial sheath, but

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not nerve capillaries, requires nerve factors to maintain a low permeability. This work was done by K. Wadhwani and C. Latker.

2. Pathophysiology of nerve edema in galactose neuropathy. K. Wadhwani demonstrated that both nerve water content and blood-nerve barrier permeability increase in rats fed high galactose diets for 11 months. The changes in water content and permeability could be completely prevented by treatment with aldose reductase inhibitors, consistent with the hypothesis that nerve edema occurs secondarily to nerve accumulation of osmotically active polyol compounds.



Employee Recognition

Byrd, Linda	Performance Award
Gillete, Jane	Performance Award
Teichberg, Diane	Quality Step Increase
Trotti, Beth	Quality Step Increase
Wagner, Elizabeth	Performance Award

Staff Accomplishments

DeCarli, Charlie      Attended the 42nd Annual Meeting of American Academy of Neurology. Miami, Florida-April 1990

Grady, Cheryl      International Neuropsychological Society Feb, 1990. Grady CL, Haxby JV, Horwitz B, Schapiro M, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Rapoport SI. Changes in regional cerebral blood flow (rCBF) demonstrate separate visual pathways for object discrimination and spatial location.

Society of Nuclear Medicine, June 1990.  
Grady CL, Haxby JV, Horwitz B, Schapiro MB, Herscovitch P, Carson RE, Rapoport, SI. Test-retest comparison of regional cerebral blood flow (rCBF) activation during a face matching task.

Haxby, James      Haxby JV, Parasuraman R, Shifting selective attention to visual features: evidence for two underlying processes. Paper presented at the Psychonomics Society, Atlanta, GA, Nov. 1989.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Schapiro MB, Rapoport SI. Relations between regional cerebral blood flow increases during visual processing and visuoperceptual performance. Journal of Clinical and Experimental Neuropsychology, 1990, 12:93-94. Presented at the North American Meeting of the International Neuropsychological Society, Orlando, FL, Feb. 7-10, 1990.

Haxby JV, Neuropsychological Investigation with Positron Emission Tomography. Department of Psychiatry, University of California at San Diego, May 7-8 1990.

Haxby JV, Mapping Human Extrastriate Cortex. In G. McKhann, P. Fox (chairs), "Functional Mapping of the Human Brain," Johns Hopkins University, Baltimore, MD, June 28-29 1990.

Horwitz, Barry      Attended lecture at Johns Hopkins University School of Medicine - Dept. Radiology Baltimore, MD, Oct. 1989, "The Use of PET to Study Functional Interactions in the Brain".

Attended Winter Conference on Brain Research, Snowmass, CO, Feb. 1990, "New Techniques for





Studying Information Flow During Visual Processing".

Attended Washington University School of Medicine, Dept. Radiology, St. Louis, MO, July, 1990, "The Use of PET to Study Functional Interactions in the Brain."

First Annual Bristol-Myers Symposium of Neuroscience Research: Integrative Functions (Mountcastle Symposium) Baltimore, MD, Oct. 11-12, 1989, Presentation: "The Relation Between Imbalances in Parietal-Frontal Functional Interactions and Attentional Dysfunction in Autism and Down Syndrome".

Annual Meeting of the Society for Neuroscience, Phoenix, AZ, Oct. 29 - 3 Nov 1989, Presentation: "A Simulation Model for Studying Interregional Correlations between Cerebral Metabolic Rates".

Annual Meeting of the Society for Nuclear Medicine, Washington, DC, June 19-22, 1990.

Morris, Pearse

Meetings of American Psychiatric Association, Society of Biological Psychiatry, and Federation of American Societies for Experimental Biology. Biological Psychiatry, and Federation of American Societies for Experimental Biology. Gave Grand Rounds at University of Calgary and Saskatachewan, Canada. Was guest-speaker at teaching seminars at Shephard-Pratt Hospital, Baltimore. Attended AFIP courses on Neuropathology and Neuroradiology. Attended Johns Hopkins seminar on PET and SPECT.

Pietrini, Pietro

Award from Societa' Italiana di Psichiatria (Italian Psychiatric Association) for a research on the effects of drug treatment on cerebral glucose metabolism in Obsessive-Compulsive Disorder patients assessed by Positron Emission Tomography.

Raffaele, Kathleen

Attended Society of Neuroscience meeting, Phoenix, Az., Oct. 29 - Nov 3, 1989 presented abstract: Raffaele, KC, Haxby JV, Morris P, Soncrant TT, and Rapoport SI, 1989. Visuo-spatial and memory function following arecoline infusion in patients with dementia of the Alzheimer type.

Salerno, Judith

Presentation: Fifth Scientific Meeting of the American Society of Hypertension, May 19, 1990. "Magnetic Resonance Abnormalities and Cerebral

Glucose Utilization in Hypertensive Men". (New York)

Appointment: Assistant Clinical Professor, George Washington University Medical Center, Division of Health Care Sciences.

Schapiro, Mark

Presented a Poster "Reductions in Panetal/Temporal Cerebral Glucose Metabolism are not Specific for Alzheimer's Disease" American Academy of Neurology May 2, 1990, Miami, FL.



Trotti, Beth

Lead User, Network Administrator for the LNS.

Weinstein, Edwin

Reduplication and the Syndrome of Capgras. Society  
for Behavioral Neurology, Miami, FL, May 1, 1990.

Attended the American Academy of Neurology  
Meeting, April 30 - May 3, 1990, Miami, FL.

LPC-IRP-NIA

EDBP-NIA



Training

Schapiro, Mark	Introduction to Cricket Graph	6/1/90	\$100
	Introduction to PC DOS	5/7,9,11/90	\$170

International Activities

DeCarli, Charles	Invited Guest, Cerebral Ischemia and Dementia International Workshop. Prien, Chiemsee/Germany June 25-28, 1990. Presented a paper on "Dementia with severe white matter changes on magnetic resonance imaging--Effect on neuropsychological testing, structural imaging and positron emission tomography".
Friedland, Robert	Attended the 13th International Symposium of the Taniguchi Foundation and to present a paper entitled, "Aging of the Brain: Cellular and Molecular Aspects of Brain Aging and Alzheimer's disease", Kyoto Japan.
Grady, Cheryl	Participant at the 5th Congress of the World Federation of Nuclear Medicine and Biology, Aug 26-31, 1990, Palais des Congres, Montreal Canada. Presenting a paper on "Test-Retest Comparison of Regional Cerebral Blood Flow (RCBF) Activation During a Spatial Location Task".
Haxby, James	Presented a paper on Differential diagnosis of dementia. Participant in the International Symposium on Cerebral Blood Flow in Cerebrovascular Disease and Dementia, Naples, Italy, September, 1989.  Presented a paper on "Cognitive Deficits and Local Metabolic Changes". Participant in a conference on Cerebral Topography and Alzheimer's Disease Lille, France, October, 16, 1989.  Presented a paper on Mapping Object and Spatial Vision Pathways in Human Extrastriate Cortex. Participant in a conference on Brain Work Imaging, Copenhagen, Denmark, August 13-16, 1990.
Morris, Pearse	Invited speaker for grand rounds at the University of Calgary, Alberta, and the University of Saskatchewan, Saskatoon, Canada. Topics for rounds was "A Trail of Arecoline in Dementia of the Alzheimer Type", October 1989.
Pietrini, Pietro	Invited participant at the international meeting Psychiatry and Advanced Technologies, Saint-Vincent, Acosta (Italy), September 25-28, 1990. The following talk will be presented "Cerebral Glucose Metabolism in Neuro-psychiatric Diseases assessed by Positron Emission Tomography (PET). Studies in dementia of the Alzheimer Type and Obsessive-Compulsive Disorder."



Schapiro, Mark

Invited Guest at the Fondation IPSEN Symposium  
entitled, Imaging, Cerebral Topography and  
Alzheimer's Disease, Lille, France 10/16/89.  
Presented a paper entitled "Topographical  
Comparisons of Lesions in Trisomy 21 and  
Alzheimer's Disease: A Study with PET, Anatomical  
and Neuropathological Investigations."

LPC-IRP-NIA

EDBP-NIA





Employee RecognitionAwards

Kelly, Judy  
 Smith, Quentin  
 Villacreses, Nelly

Performance Award  
 NIH Merit Award  
 Performance Award

Staff Accomplishments

Murphy, Vince

Attended FASEB Meeting,  
 Washington, D.C.; April 1-5,  
 1990; presented abstract entitled  
 "Elevation of brain manganese in  
 rats fed low calcium diets".

Attended ASPET Meeting;  
 Milwaukee, WI; August, 1990; will  
 present abstract entitled  
 "Concentration dependence of  
 manganese influx into brain".

Rosenberg, Jack

Attended the FASEB Meeting,  
 Washington, D.C.; April 1-5.  
 Presented a abstract entitled  
 "Chronic Hypocalcemia Alters  
 Bile Manganese Excretion".

Smith, Quentin

Attended FASEB Meeting,  
 Washington, D.C., April, 1990.

Wadhvani, Kishena

Attended Society for Neuroscience  
 Annual Meeting in October 1989.  
 "L-Pherryldamine transport  
 across the blood-nerve barrier is  
 stereospecific, saturable and  
 sodium independent."

Training

Best, Donetta	Domestic Travel	1/8/90-1/12/90	\$210
	Introduction to WP5.0	1/23/90-1/26/90	\$125
	Basic Time and Attendance	2/1/90-2/2/90	\$125
	Creating & Using Simple Wylbur Command Procedures	Spring 1990	\$150
	Introduction to Wylbur	Spring 1990	\$150
	Introduction to NIH for New Support Staff	7/16/90-7/20/90	\$360
Takada, Yoshiaki	Radiation Safety in the Laboratory	Fall 1989	\$60
Villacreses, Nelly	Introduction to WP Neurochemistry	3/15-16/90 1/23-5/18/90	\$200 \$158



International Activities

Smith, Quentin

Invited Speaker-1st Toronto-Stockholm Symposium on Perspectives in Diabetes Research: University of Toronto, Canada, June 28-29, 1990. Presented paper "Metabolism and Transport of Amino Acids".

Invited Speaker-Symposium on the Brain Capillary Endothelium, London, England, December 1989, Presented talk-"The blood-brain barrier-New perspectives with the brain perfusion technique".

Attended the 19th Annual Meeting of the Society for Neuroscience in Phoenix Arizona from Oct 29 - Nov 3, 1989 and presented the paper: "Structural specificity of the brain capillary neutral amino acid transporter."

Invited Speaker at a Preuss Foundation Symposium entitled "Role of the Blood-Brain Tumors", which was held in Scottsdale, Arizona from Nov. 3-4, 1989. I gave a presentation entitled, Carrier-mediated delivery of amino acid analogues through the blood-brain barrier."



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00126-10 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Function in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. Schapiro	Chief, SBAD	LN, NIA
	C. Grady	Chief, Unit on PET	LN, NIA
	B. Horwitz	Research Mathematician	LN, NIA
	J. Haxby	Research Psychologist	LN, NIA
	J. Salerno	Medical Staff Fellow	LN, NIA
	D. Murphy	Visiting Associate	LN, NIA
	P. Pietrini	Visiting Associate	LN, NIA
	A. Gonzalez-Aviles	Medical Staff Fellow	LN, NIA

## COOPERATING UNITS (if any)

Child Psychiatry, NIMH; Department of Nuclear Medicine, CC; Laboratory of Neuro-  
psychology, NIMH; Clinical Brain Disorders Branch, NIMH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging &amp; Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1.9

## PROFESSIONAL:

1.9

## OTHER:

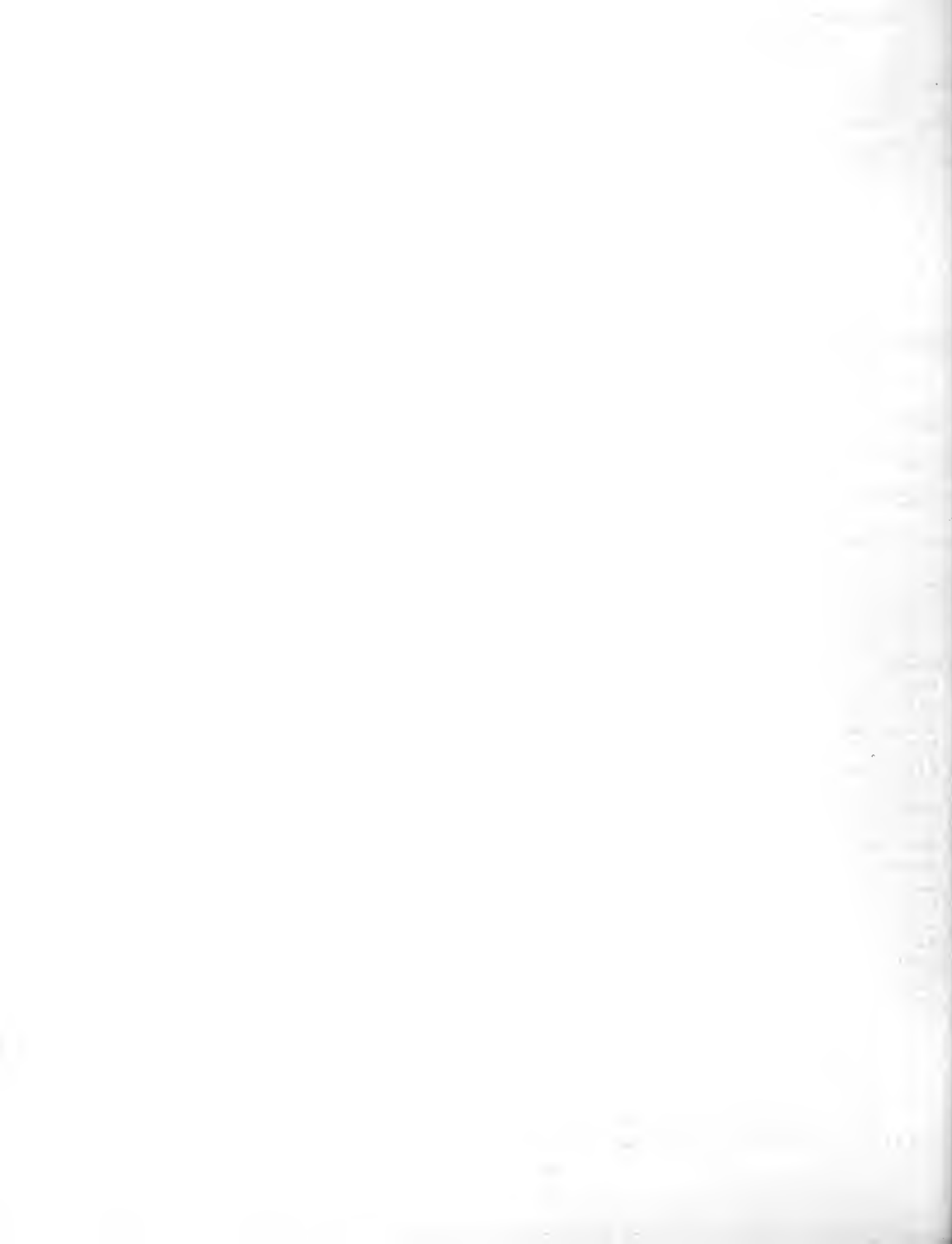
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## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Using a high resolution PET scanner, whole brain glucose use decreased with age by 12% between 20-90 years. No effect of gender on metabolism was found in young subjects. Analysis of high resolution PET data in dementia of the Alzheimer type (DAT) replicated earlier findings of relative metabolic deficits in association neocortex, and increased the ability to see differences in absolute rates. Four subgroups of DAT patients were identified based on metabolic patterns. A longitudinal study of three monozygotic twin pairs discordant for DAT showed continued discordance in metabolic indices indicating the importance of non-genetic factors in the disease. DAT patients with frontal lobe behavioral syndromes had significant decrements in frontal lobe metabolism compared to other DAT patients but were not impaired on tests of frontal cognitive function. Activation of regional cerebral blood flow demonstrated a parietal visual system for spatial location and an occipito-temporal system for object identification in both young and old healthy subjects. Patients with trichotillomania, a disease similar to obsessive-compulsive disorder, were compared to age matched controls and found to have higher rCMRglc in all cortical regions. Healthy young Down syndrome adults do not have abnormal regional or global cerebral blood flow or glucose metabolism prior to the age at which the neuropathological changes of Alzheimer's disease occur. Regional cerebral metabolism was reduced in older as compared to younger adults with Down syndrome, and similarities between DAT and dementia in Down syndrome were demonstrated.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00128-10 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analytical Drug Methods

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	N. Greig	Guest Researcher	LN, NIA
	L. Hegedus	Visiting Associate	LN, NIA
	J. Deutsch	Visiting Scientist	LN, NIA
	H. U. Shetty	Guest Researcher	LN, NIA

Others:	E. Daly	Chemist	LN, NIA
	G. Phelan	IRTA Fellow	LN, NIA
	S. I. Rapoport	Chief	LN, NIA

## COOPERATING UNITS (if any)

Athena Neurosciences, Inc., San Francisco, CA

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

3.0

## PROFESSIONAL:

2.0

## OTHER:

1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

An analytical method using high performance liquid chromatography (HPLC) with ultraviolet detection was developed for the measurement of bromocriptine, a dopaminergic agonist, in plasma and brain of rats. HPLC assays for chlorambucil and lipophilic derivatives were developed. Gas chromatographic/mass spectrometric assays for arecoline and scopolamine in rat plasma and brain and in human plasma were developed. The age-dependent pharmacokinetics of metachlorophenyl-piperazine, a serotonin autoreceptor agonist, were determined in rats.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00129-10 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Distribution of Nutrients, Metals and Toxins within the Central Nervous System

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Q. R. Smith	Section Chief	LN, NIA
	V. Murphy	Senior Staff Fellow	LN, NIA
	J. Rosenberg	NRC Fellow	LN, NIA
	Y. Takada	Visiting Fellow	LN, NIA

Others:	S. I. Rapoport	Laboratory Chief	LN, NIA
	R. Schwarcz	Director	Maryland Psychiatric Res. Center

## COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NIMH; Unit on Neurotoxicology, INSERM, Paris, France;  
Neuroscience Laboratory, Maryland Psychiatric Research Center; Tokyo Medical and  
Dental University, Tokyo, Japan; Office of Scientific Director, NINDS

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Neurochemistry and Brain Transport

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

4.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

An electron beam x-ray microanalysis method was developed to examine the cellular and regional distribution of metals in unfixed, unstained, fresh-frozen human brain tissue. Analysis of samples from patients with Alzheimer's disease demonstrated that neither aluminum, calcium or silicon is accumulated significantly in senile plaques as compared to surrounding brain tissue or brain tissue from aged-matched controls.

Rates of entry of selected metals into the central nervous system were determined in awake, unanesthetized rats following intravenous administration. Values were found to differ among metals by at least two-orders of magnitude with lead > calcium = cadmium > gallium for uptake into brain. Calcium influx into cerebrospinal fluid is maintained constant during chronic hypocalcemia by a saturable, vitamin D-independent transport mechanism at the choroid plexus epithelium. Low dietary calcium was shown to facilitate manganese uptake and deposition in brain.

Essential nutrients that are required for brain metabolism are transported into brain from plasma by specific, saturable transport mechanisms at the blood-brain barrier. A brain perfusion technique was used to characterize the transport systems for glucose and amino acids and to evaluate the structural specificity of the neutral amino acid transport system. The availability of albumin-bound tryptophan for uptake into brain was found to be dependent on the cerebral perfusion rate.

The rate of transport of neutral amino acids into brain was found to decrease during development and then remain constant with age in the rat. The pattern of amino acid transport matched that of brain protein synthesis, suggesting that blood-brain barrier transport capacity is modulated to meet the metabolic needs of the brain.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00134-07 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Lipid Metabolism, Relation to Function and Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Purdon	Guest Scientist	LN, NIA
	W. Williams	NRC Associate	LN, NIA
	L. Freed	Guest Scientist	LN, NIA
Others:	T. Nariai	Visiting Fellow	LN, NIA
	N. Greig	Guest Scientist	Athena Neurosci.
	S. Genka	Guest Scientist	Athena Neurosci.
	B. Schmall	Research Chemist	Dept.Nuc.Med., CC

## COOPERATING UNITS (if any)

Dept. Nuclear Medicine, Clinical Center; Athena Pharmaceutical, San Francisco;  
Dept. Biochem., Creighton University

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland, 20892

## TOTAL MAN-YEARS:

4

## PROFESSIONAL:

4

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Using radiolabeled fatty acids, a mathematical model was developed to calculate transfer constants ( $k^*_{FFA}$ ) and rates of incorporation ( $J_{FFA}$ ) of plasma free fatty acids into individual brain regions.

3H-palmitic acid (PA) is incorporated into the sn-1 position of phosphatidylcholine;  $^{14}C$ -arachidonic acid (AA) is incorporated into the sn-2 position of phosphatidylinositol and phosphatidylcholine;  $^{14}C$ -docosahexaenoic acid (DHA) is incorporated into the sn-2 position of phosphatidylethanolamine.

The incorporation of 3H-AA and  $^{14}C$ -DHA, but not 3H-PA, into brain lipids increased in rats give arecoline, a cholinergic agonist. Regional increases were greater in brain areas with  $M_1$ , receptors which are linked to phospholipid turnover.

Incorporation of 3H-PA into intracerebrally implanted Walker 256 carcinosa was 3-6 fold higher than control brains in rats. Incorporation of  $^{18}F$ -dl-erythro-9,10-difluoropalmitate into brain phospholipids was similar to that of  $^{14}C$ -PA. Therefore, this tracer may be a useful probe for studying brain lipid metabolism in humans with positron emission tomography.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00403-05 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Genetics of Alzheimer's Disease

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Carol Fuchs, MSW	Social Worker	LN, NIA
	Mark Schapiro	Senior Staff Fellow	LN, NIA
Others:	Anand Kumar	Medical Staff Fellow	LN, NIA
	Beverly White	Medical Res. Officer	LCB, NIDDK
	Katherine Sanford	Chief, In Vitro Carc.	LCMB, NCI
	Ram Parshad	Professor	Howard Univ.
	K. Chandrasekaran	Visiting Scientist	LN, NIA

## COOPERATING UNITS (if any)

LCMB, NCI; Department of Pathology, Howard University; LCB, NIDDK; Harvard University

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

3.0

## PROFESSIONAL:

1.5

## OTHER:

1.5

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Pedigrees were constructed from the family histories of all patients participating in the dementia program in order to examine the genetic basis of Alzheimer's disease.

Differences in family history between monozygotic twins discordant or concordant for dementia of the Alzheimer type suggest heritable and nonheritable forms of Alzheimer's disease.

Collaborative studies were established to examine the ability of peripheral blood lymphocytes of probands with Down syndrome and familial Alzheimer's disease to repair X-irradiation induced damage during the G2 period of the cell cycle, and for the Down syndrome subjects, to see if the parents' lymphocytes show chromosomal instability.

Efforts continue to evaluate genetic aspects of presenile dementia. Specifically, secondary sex chromosomal variation, alpha-1-antitrypsin (PI) phenotyping, and cytological analysis of variations in the Nucleolus Organizing Regions (NOR) were analyzed.

Hind III digests of southern blots of genomic DNA from 4 sets of identical twins were obtained. Analysis with the polymorphic DNA marker D2IS52 showed that all sets of twins were identical.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AC 00121-13 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Function and Structure of Peripheral Nerve

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	K. C. Wadhvani	Staff Fellow	LN, NIA
	Q. R. Smith	Section Chief	LN, NIA

Others:	S. I. Rapoport	Laboratory Chief	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA
	E. Rechthand	Senior Staff Fellow	LN, NIA
	A. Balbo	Technician	LN, NIA

## COOPERATING UNITS (if any)

US Uniformed Health Services

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Neurochemistry and Brain Transport

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2	PROFESSIONAL: 1.5	OTHER: 0.5
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## CHECK APPROPRIATE BOX(ES)

- ☐ Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Blood-nerve barrier permeability to ions and nonelectrolytes is very low, indicating limited exchange between plasma and nerve endoneurium. The nerve barrier, unlike the brain barrier, appears not to have a regulatory transport system for calcium. As a result, nerve calcium concentration varies with the plasma calcium concentration.

Glucose and amino acids are taken up into nerve from plasma by facilitated transport systems located at the endoneurial endothelium. The transport systems accelerate nerve uptake of nutrients, and allow matching-of transport to metabolic demand.

Permeabilities of both nerve capillaries and perineurium increase during the first few weeks following nerve damage and Wallerian degeneration. Nerve capillary permeability eventually returns to normal, but perineurial permeability remains elevated, suggesting that nerve fibers are required to maintain perineurial nerve barrier integrity.

Blood-nerve barrier permeability and nerve water content were found to increase in rats fed high galactose diets for 11 months. Both changes could be prevented by treatment with aldose reductase inhibitors, such as Statil and Alconil, consistent with the "polyol" hypothesis of galactose neuropathy.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00123-12 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neuronal Development in Tissue Culture

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. Ault	Senior Staff Fellow	LN, NIA
	P. Caviades	Visiting Fellow	LN, NIA
	E. Coan	Visiting Fellow	LN, NIA
	Z. Galzicki	Visiting Associate	LN, NIA
Others:	A. Balbo	Biological Technician	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA
	A. Fine	Associate Professor	Univ. of Dalhousie
	C. Epstein	Professor of Pediatrics	UCSF

## COOPERATING UNITS (if any)

University of Dalhousie, Nova Scotia, Canada; Department of Pediatrics, Univ. of California, San Francisco, CA; Department of Biochemistry, Creighton Univ., Omaha, NE

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.5

## PROFESSIONAL:

2.5

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cultured dorsal root ganglion (DRG) neurons from fetal trisomy 19 mice showed no difference in electrical membrane properties compared to neurons from littermate controls, indicating that these parameters are not altered generally in trisomies. DRG neurons transgenic for the human gene for superoxide dismutase (found on human chromosome 21 and mouse chromosome 16) showed no significant difference in action potential parameters compared to control cells, indicating that excess dosage of this gene alone does not underlie abnormalities identified in trisomy 16 and trisomy 21 neurons.

In replated trisomy 21 fetal neurons, voltage clamp studies identified tetrodotoxin-sensitive and slow tetrodotoxin-insensitive sodium currents, the latter accounting for 90% of the total charge moving across the membrane. No alterations in maximal conductances were observed. The slow sodium component had slowed deactivation kinetics. Inactivation curves for both fast and slow currents were shifted 10 mV in the depolarizing direction in trisomy 21 neurons, resulting in a greater number of sodium channels available for activation. Nerve growth factor (NGF) was shown to be essential for the survival of human fetal neurons in culture, but not responsible for the differences in electrical membrane properties observed between trisomy 21 and control neurons.

Fetal brain tissue from the trisomy 16 mouse was shown to survive for 14-24 weeks after being grafted into host mouse brain, thus providing a possible animal model of Alzheimer's disease.

Fluorescence studies of catecholamines suggested that trisomy 16 neurons have abnormal neurotransmitter uptake.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER  
Z01 AG 00125-12 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebral Metabolism, Relation to Brain Function and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	E. DeMicheli	Visiting Fellow	LN, NIA

Others:	H. Holloway	Biologist	LN, NIA
	D. Larson	Biologist	LN, NIA
	N. Greig	Guest Researcher	Athena Neurosciences
	U. Freo	Visiting Fellow	LN, NIA
	J. Atack	Visiting Associate	LN, NIA

## COOPERATING UNITS (if any)

Department of Neuropathology, Univ. Western Ontario; Laboratory of Clinical Sciences, NIMH; Laboratory Analytical Chemistry, NIDDK; Athena Neurosciences

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

5.5

## PROFESSIONAL:

3.0

## OTHER:

2.5

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The regional cerebral metabolic rate for glucose was measured with the [<sup>14</sup>C]2-deoxy-D-glucose technique in young and aged male Fischer-344 rats, following administration of cholinergic (arecoline), dopaminergic (haloperidol, bromocriptine), and serotonergic (m-chlorophenylpiperazine) drugs. For arecoline, the absence of age differences in most brain areas indicated that muscarinic receptor mechanisms are intact in the senescent rat brain. Responses to bromocriptine and haloperidol were reduced in senescent as compared to younger rats, suggesting reduced central dopaminergic function, and an imbalance between cholinergic and dopaminergic systems. Aged rats displayed reduced responsivity to m-chlorophenylpiperazine, indicating an age-dependent functional defect in serotonergic neurotransmission. A model of cholinergic cortical deafferentation was implemented in rats, lesioning the nucleus basalis magnocellularis. Initial cerebral metabolic deficits returned to normal within two weeks after lesioning in young rats.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00120-13 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Blood-Brain Barrier and Central Nervous System Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: N. H. Greig

Guest Researcher

LN, NIA

Others:

S. Genka

Guest Researcher

LN, NIA

H. Shetty

Guest Researcher

LN, NIA

S. I. Rapoport

Chief

LN, NIA

T. Soncrant

Senior Staff Fellow

LN, NIA

R. Rothman

Unit Chief

LCS, NIMH

V. John

Scientist

Athena Neurosciences

## COOPERATING UNITS (if any)

LCS, NIMH; LCS, NIAAA; Athena Neurosciences Inc., San Francisco, CA;  
Proctor & Gamble, Cincinnati, OH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

4.5

PROFESSIONAL:

3.5

OTHER:

1

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Longitudinal analysis of the most recently available data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program demonstrated a dramatic rise in the age-specific incidence of primary malignant brain tumors in the elderly between 1973 and 1985, in the United States. Primary malignant brain tumors have perhaps the worst prognosis of all cancers. They are invariably fatal, with a median survival time of approximately 10 months.

Rational strategies were developed to improve the treatment of malignant brain tumors. A novel lipophilic anticancer alkylating agent, a tertiary butyl ester of chlorambucil, was developed for brain tumor treatment. It has a high delivery to brain and efficacy against brain tumor cells. Further, a blood-brain barrier opening technique was developed to increase the brain delivery of water-soluble therapeutic agents. The intracarotid infusion of a hypertonic solution of either mannitol or L-arabinose causes transient and innocuous barrier opening allowing increased uptake of therapeutics and intravascular markers into brain. A mathematical model describing drug uptake into brain tumors, directly from blood and indirectly from neighboring tissue, was developed and used to quantitate the effectiveness of the osmotic method. The factors that codetermine the amount of drug that enters and is maintained in brain following its systemic administration were analyzed to aid in the development of central nervous system therapeutics.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00132-06 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Anatomy in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. DeCarli Senior Staff Fellow LN, NIA  
B. Horwitz Chief, Unit on Brain Imaging & LN, NIA  
Computers  
D. Murphy Visiting Associate LN, NIA

Others: M. Schapiro Chief, BADS LN, NIA  
S. I. Rapoport Chief LN, NIA  
W. Kozachuk Visiting Associate LN, NIA  
L. Levy Guest Researcher NIS, NINDS

## COOPERATING UNITS (if any)

LNC, NIMH; NIS and DIR, NINDS; CC Radiology; DCT/PB, NCI; General Electric

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1

## PROFESSIONAL:

1

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☒ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The transverse computer assisted tomography (CT) method of calculating ventricular volumes of the human brain in vivo, using TRACE image analysis procedure was found to be highly reliable, and suitable for longitudinal studies of aging and dementia.

Quantitative CT analyses in healthy aging men and women demonstrated significant sex differences in ventricular volume and in age of onset of ventricular enlargement. Structural brain changes, as measured by ventricular enlargement, and decline in cognitive performance on the Wechsler Adult Intelligence Scale (WAIS) appear to be relatively independent processes correlated more to the age of the subject. Three sets of monozygotic twins discordant for Dementia of the Alzheimer type (DAT) were studied and found to have significant differences in cross sectional ventricular volumes and rates of ventricular enlargement that were abnormal.

Eight children with AIDS encephalopathy were studied and found to have significant reductions in the ventricular brain ratio (VBR), accompanied by improvement of cognitive function, when treated with continuous infusion of azidothymidine (AZT) for six months.

Magnetic resonance imaging (MRI) can be used to evaluate temporal lobe and peripheral cerebral spinal fluid (CSF). MRI analyses also revealed significant reduction in the width of the pars compacta of the substantia nigra in patients with extrapyramidal Alzheimer's disease. The prevalence of white matter hyperintensities identified on T2 weighted axial MRI images is increased with healthy aging. White matter hyperintensities were not more frequent in DAT patients when compared to age matched controls.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00133-08 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Pharmacokinetics, Pharmacodynamics and Therapeutics

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Senior Staff Fellow	LN, NIA
	K. Raffaele	Staff Fellow	LN, NIA
	J. Haxby	Senior Staff Fellow	LN, NIA
Others:	A. Kumar	Medical Staff Fellow	LN, NIA
	P. Morris	Visiting Associate	LN, NIA
	J. Atack	Visiting Associate	LN, NIA
	N. Greig	Guest Researcher	Athena Neurosciences

## COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NIMH; Section of Clinical Psychopharmacology, NIMH;  
Human Motof Control Section, NINDS; College of Pharmacy, Univ. of Saskatchewan;  
Athena Neurosciences, Inc., San Francisco

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIA, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

1.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Biopterin administration to some subjects with Alzheimer's disease elevated cerebrospinal fluid biopterin values to age-matched normal values. Biopterin appeared also to increase central dopamine turnover in these subjects, suggesting that biopterin deficiency leads to impaired dopaminergic neurotransmission in a subset of Alzheimer's subjects.

Administration of haloperidol, a dopamine antagonist, produced greater cognitive and motor effects in young than in aged healthy men; suggesting that responsiveness of the brain dopamine system is reduced with age in humans.

Brain dopamine turnover, as measured with the debrisoquin method, is reduced in aged compared to young healthy adult males.

Arecoline, a cholinergic agonist, can be administered safely to humans and has favorable pharmacokinetic properties for clinical studies in Alzheimer's disease.

REPORT OF THE  
COMMISSIONER OF THE  
LAND OFFICE  
FOR THE YEAR  
1900

STATE OF NEW YORK  
LAND OFFICE  
ALBANY  
JANUARY 1, 1901

REPORT OF THE  
COMMISSIONER OF THE  
LAND OFFICE  
FOR THE YEAR  
1900

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00135-07 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Biology of Brain Aging and Disease

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	K. Chandrasekaran	Visiting Scientist	LN, NIA
	J. Stoll	Staff Fellow	LN, NIA
	T. Giordano	Staff Fellow	LN, NIA
Others:	J. R. Atack	Visiting Associate	LN, NIA
	S. P. Wise	Chief	LNP, NIMH
	M. Bustin	Chief	MC, NCI
	M. F. Matocha	Senior Staff Fellow	LN, NIA

## COOPERATING UNITS (if any)

Laboratory of Neurophysiology, NIMH; Laboratory of Molecular Carcinogenesis, NCI

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.25

## PROFESSIONAL:

2.25

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

cdna libraries were prepared using mRNAs isolated from specific regions of the brain of the Rhesus monkey. Differential hybridizations were carried out to identify cdna clones corresponding to genes predominantly expressed in either association or primary sensory neocortical areas.

Total RNA was isolated from control and trisomy 16 mouse tissue.

The polyadenylated fraction was isolated and used for Northern blot hybridization analysis to quantitate the expression of various genes located on mouse chromosome 16.

The activity of the protein product (tyrosine protein kinase) of the src oncogene was measured in whole brain of Fischer-344 rats by an in vitro immune complex kinase assay. There was no significant difference in the pp60c-src specific kinase activity as a function of age.

The gene for high-mobility-group (HMG) chromosomal protein HMG-14, which is located in region 21q22.3 of human chromosome 21 (obligated Down syndrome region) was identified on mouse chromosome 16; HMG-14 is expressed 1.5 times normal in mouse trisomy 16, a model for human trisomy 21.

Increased numbers of extra-adrenal chromaffin cells of abdominal paraganglia of senescent Fischer-344 rats are not to due cell proliferation, but to induction from pre-existing cells via glucocorticoids.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00140-07 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebrospinal Fluid Chemistry in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. R. Atack	Visiting Associate	LN, NIA
	S. I. Rapoport	Chief	LN, NIA

Others:	J. DeGeorge	Senior Staff Fellow	LN, NIA
	C. May	Medical Staff Fellow	LN, NIA
	T. Soncrant	Senior Staff Fellow	LN, NIA
	M. B. Schapiro	Senior Staff Fellow	LN, NIA
	E. Daly	Chemist	LN, NIA

## COOPERATING UNITS (if any)

Laboratory of Neurochemistry, NIMH; Department of Pharmacology and Experimental Therapeutics, Loyola University; Department of Neurology, Massachusetts General Hospital, Boston, MA

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia/Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland, 20892

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

1.4

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Subtypes of dementia of the Alzheimer type (DAT) - DAT with motor abnormalities, such as extrapyramidal signs (EDAT) and myoclonus (MDAT), were studied using neurochemical measurements in the cerebrospinal fluid (CSF). Reductions in somatostatin-like immuno-reactivity (SLI) and acetylcholinesterase (AChE) activity were found in DAT, EDAT and MDAT. An inverse relation between CSF HVA and alpha-MSH-LI was found in DAT patients. Furthermore, in patients with Parkinson's disease, CSF alpha-MSH-LI was elevated. Young adult Down syndrome subjects had elevated levels of CSF choline, but AChE activity and somatostatin and neuropeptide Y concentrations did not differ from control values in either young or old Down patients. In healthy control subjects, age-related increases were found in CSF total protein, choline, the polyols erythritol and myoinositol, and AChE activity. CSF production is reduced in healthy old subjects.

The rate of formation of CSF in elderly subjects (0.2 ml/min) was 50% that of young subjects (0.4 ml/min). CSF protein gradients did not differ between young and old subjects. There was no significant difference in rostrocaudal CSF gradients of somatostatin or neuropeptide Y caudal lumbar CSF fractions, whereas AChE activity was higher in the more caudal fractions of young but not old subjects.

LPC-IRP-NIA

EDBP-NIA



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00131-08 LN

LPC-IRP-NIA

EDBP-NIA

PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. Grady Research Psychologist LN, NIA

Others: M. Schapiro Chief, SBAD LN, NIA  
Q. Devinsky Medical Staff Fellow CNB, NINDS  
S. Sato Chief, EEG Lab CNB, NINDS

COOPERATING UNITS (if any)

CNB, NINDS

LAB/BRANCH

Laboratory of Neurosciences

SECTION

Brain Aging and Dementia

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

1.0

PROFESSIONAL:

.5

OTHER:

.5

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard un-reduced type. Do not exceed the space provided.)

Basal Metabolic Rate (BMR) was measured in young subjects with Down Syndrome (DS) and healthy controls to see if extra genomic material affects basal metabolism. No difference was found between DS subjects and controls, suggesting that chromosome 21 does not control BMR.

The relation of EEG (electroencephalogram) alpha background to cognitive function and cerebral metabolism was assessed in young and old DS subjects. Old DS subjects with decreased alpha backgrounds had dementia, reduced cognitive function, larger ventricles, and a global decrease in cerebral glucose utilization compared to age-matched subjects with normal alpha backgrounds. In contrast, the EEG background did not correlate with psychometric or brain metabolic data in the younger DS subjects.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00404-04 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Functional Interactions Among Brain Regions in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: B. Horwitz Research Mathematician LN, NIA

Others:

T. Soncrant	Senior Staff Fellow	LN, NIA
C. L. Grady	Research Psychologist	LN, NIA
M. B. Schapiro	Chief, BADS	LN, NIA
J. V. Haxby	Research Psychologist	LN, NIA
N. Azari	NRC Fellow	LN, NIA
L. Ungerleider	Research Psychologist	LN, NIMH

## COOPERATING UNITS (if any)

DMN, CC; NIMH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

1.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A correlation method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose as determined by positron emission tomography in humans. The method was applied to regional metabolic data obtained by positron emission tomography (PET) from 14 young adult patients with Down Syndrome and 24 matched control subjects. Compared with controls, the Down Syndrome group had lower values for many correlations within and between the frontal and parietal lobes (including Broca's speech area), indicating a disruption of neural systems as-associated with language and with attention in Down Syndrome.

The correlation matrix method was applied to analyze glucose metabolic rates in awake Fischer-344 rats. Correlations between rCMRglc in cholinergic nuclei and frontoparietal cortex increased in rats 2 weeks after ibotenic acid lesions of the cholinergic nucleus basalis magno-cellularis, indicating altered functional interactions between the remaining cholinergic nuclei and cortex.

The correlation method was applied to rCBF data obtained in humans with PET during two visual processing tasks: face matching and dot location following rotation. Correlations among appropriate posterior brain regions were significantly large on the right side of the brain, but not on the left, although rCBF was bilaterally increased during the tasks, suggesting that these tasks are performed to a greater degree by the right posterior hemisphere than by the left.

A computer simulation model was developed to partially validate the correlational analysis as applied to metabolic data, demonstrating that correlational analysis yields information on regional involvement in neural systems not evident in the pattern of absolute metabolic values.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00405-04 LN

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

New Investigations in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. Schapiro	Senior Staff Fellow	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA
	C. DeCarli	Senior Staff Fellow	LN, NIA
	W. Kozachuk	Medical Staff Fellow	LN, NIA
	J. Salerno	Senior Staff Fellow	LN, NIA
Others:	M. Hertzman	Professor of Psychiatry	George Washington Univ.
	S. Rapoport	Chief	LN, NIA

## COOPERATING UNITS (if any)

George Washington University; Department Psychiatry, Laboratory of Central Nervous System Studies, NINDS; School of Medicine, University of Colorado, Laboratory Chemical Biology, NIDDK; Division of Neurology, Dept. of Med., Duke Univ.

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia Section

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.0

## PROFESSIONAL:

2.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

A number of new protocols were introduced to examine brain aging and cerebral metabolism. In using the isotope fluoro-18-deoxyglucose with positron emission tomography, we found that cerebral glucose utilization does not change with advancing age in healthy males, but changes are found in patients with Alzheimer's disease and Down syndrome. Three new protocols allow us to evaluate these findings and determine their specificity. Studies are underway in multi-infarct dementia, the second leading cause of dementia; a major depressive disorder both with and without cognitive impairment; and fragile-X syndrome to evaluate PET alterations uncovered in our laboratory in subjects with Down syndrome.

The role of the dopaminergic system in normal aging, Alzheimer's disease with and without extrapyramidal signs, and familial inverted chorea will be explored with 6-[18-F]-fluoro-L-Dopa (6-FD) and positron emission tomography (PET).



LPC-IRP-NIA

EDBP-NIA



# ANNUAL REPORT OF THE LABORATORY OF PERSONALITY AND COGNITION

## NATIONAL INSTITUTE ON AGING

1989-1990

### Overview

The fundamental scientific paradigm which guides research in the Laboratory of Personality and Cognition (LPC) is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ--in health, in rates of aging, in cognitive ability, in personality, in happiness and life satisfaction. The mission of the LPC is threefold: (1) to conduct basic and clinical research on individual differences in cognitive and personality processes and traits; (2) to investigate the influence of age on these variables and their reciprocal influence on health, well-being, and adaptation; and (3) to employ longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

### Cognition and Neuropsychology

Since the retirement of the Chief, Cognition Section, research on cognition has continued in this Laboratory, with a new emphasis on neuropsychological testing and the detection of early signs of Alzheimer's Disease. In collaboration with an FSKMC neurologist and with other GRC investigators, LPC scientists have begun a prospective study of the natural history of dementia in the Baltimore Longitudinal Study of Aging. This study will capitalize on archival data on cognitive performance and personality traits which can be used as long-term predictors of Alzheimer's Disease in participants who subsequently develop this disease. A sophisticated battery of neuropsychological tests is administered to BLSA participants over age 60 to detect early signs of cognitive decline.

Two papers accepted for presentation at the National Academy of Neuro-psychology Convention reflect progress on this project. The first involved immediate and 2 minute delayed free recall performance among 155 BLSA men and women as longitudinal predictors of cognitive status. Both immediate and delayed recall performance were significantly correlated with subsequent mental status, as measured by the Mini-Mental Status Examination (MMSE) and the Blessed Mental Status Test (BMST) on average 3 and 9 years later. Multiple regression analyses showed that the delayed recall measure did not appear to add to the longitudinal predictive power of immediate recall, although that may be due to the brief delay interval used. Ongoing and future longitudinal research will seek to determine whether the short-term memory task performance is an early predictor of cognitive decline and/or brain disease.





The second study examined the relationship between recognition memory performance in the Grober-Buschke Cued Selective Recall (CSR) test with two measures of cognitive status, the MMSE and the BMST. One view of normal cognitive aging holds that age declines in memory performance are due to declines in central processing resources. Because they require fewer processing resources, recognition memory tasks would thus not be sensitive indicators of age effects. Impairments in recognition memory after multiple exposures as the CSR test provides, however, may be sensitive to cognitive impairments that are not characteristic of normal aging. Subjects were 336 male and female BLSA participants, 169 of whom had taken Army Alpha IQ and verbal fluency tests an average of 23 years prior to the MMSE and BMST tests. Recognition accounted for 47% and 48% of the variation in the concurrent MMSE and BMST. Recognition also accounted for 33% and 34% of the variation in MMSE and BMST after removing 24% and 21% of the variation due to the age, education, vocabulary, IQ and fluency tests. Deficits in recognition memory performance were thus shown to be important and independent indicators of mental status. This Laboratory's ongoing research will explore the implications of these findings for the neuropsychological assessment and diagnosis of cognitive aging and brain disease.

The selection and recruitment of a new Chief of the Cognition Section has been a major priority this year. We are delighted to report that Dr. Herbert Weingartner, a distinguished Professor of Psychology at George Washington University, has accepted the position, and is scheduled to assume his duties within the Laboratory on October 1, 1990.

#### Basic Research on Personality Structure

The Five-Factor Model of personality has become the cornerstone of research for the Personality, Stress and Coping Section (PSCS). The five dimensions of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness form a comprehensive framework for conceptualizing individual differences in basic emotional, interpersonal, experiential, attitudinal, and motivational styles. The five factors are stable over time, show agreement between self-reports and raters, and capture the basic dimensions underlying such prominent personality instruments as the Guilford-Zimmerman Temperament Survey, the Eysenck Personality Questionnaire, the Myers-Briggs Type Indicator, and the California Psychological Inventory. In the past year, investigators have continued to refine their conceptions of the factors and broadened their applications. For example, an IRTA Fellow in the Laboratory completed two studies showing that two alternative measures of motivation could be understood in terms of these basic trait dimensions.

Perhaps the largest advance was in the conceptualization and measurement of facets of Agreeableness and Conscientiousness. Although there is wide agreement among personality psychologists on the general nature of these two dimensions, relatively little attention had been given to the specific traits that define them. Based on a review of the literature, PSCS researchers identified six facet traits for each. Agreeableness is expressed in the traits of Trust, Sincerity, Altruism, Compliance, Modesty, and Tender-Mindedness; Conscientiousness is seen in Competence, Order,



Dutifulness, Achievement, Self-Discipline, and Deliberation. Preliminary scales to measure these facets were constructed and showed moderate to good levels of reliability and validity in a sample of adult men and women. Revisions of these scales have now been administered to men and women in the BLSA; peer ratings have also been gathered. Measurement of these facets can advance our understanding of personality in several ways, particularly in the area of health psychology: Previous research has shown that Agreeableness vs. Antagonism is a predictor of coronary disease; in the future, it will be possible to determine which specific facets of Agreeableness are linked to heart disease.

Interest in the Five-Factor Model extends well beyond this Laboratory. One indication of the importance of the model was the decision by the editors of the Journal of Personality to devote a Special Issue to the topic. The Guest Editor of this issue is Dr. Robert McCrae, a senior investigator in LPC; ten other contributors are preparing articles on such diverse topics as abnormal, developmental, and evolutionary personality psychology. The basic research conducted in this Laboratory appears to have applications in a number of different areas.

#### Clinical Applications of Personality Research

Problems in mental health and adjustment--from depression and anxiety to marital and sexual difficulties--are faced by adults of all ages. One of the important applications of LPC research on personality, stress, and coping is in the guidance it can offer to counselors, clinical psychologists, and psychiatrists. This year Laboratory investigators continued collaborative work with a number of clinicians in a program designed to examine and document the psychotherapeutic utility of personality assessment using the NEO Personality Inventory (NEO-PI), a measure of the Five-Factor Model.

One outcome of this work was an invitation to the Chief, LPC, to serve as Guest Editor for a Special Section of the Journal of Personality Assessment on the clinical use of the Five-Factor Model. Papers in this section will document the validity of the NEO-PI in various clinical samples, describe ways in which personality information is used by practicing clinicians, and suggest hypotheses for clinical research. For example, one author argues that techniques such as guided imagery may be more effective for patients high in Openness to Experience; biofeedback may be more appropriate for patients who are low in Openness. Research testing such hypotheses is in progress.

LPC researchers have been asked to contribute articles to both the Journal of Counseling and Development and Psychological Assessment:-- A Journal of Counseling and Clinical Psychology on the use of the Five-Factor Model in counseling and clinical settings. Finally, the Chief, LPC, is co-editing a volume (with Dr. Thomas Widiger of the University of Kentucky) on Personality Disorders and the Five-Factor Model of Personality, which will be published by the American Psychological Association, and which may ultimately have an influence on psychiatric nosology in the area of the personality disorders.

#### Aging, Stress, and Coping



Researchers in PSCS have long been recognized as leaders in the longitudinal analysis of personality. This year the Chief, LPC, was invited to present a lecture as part of the Nebraska Symposium on Motivation's series on Psychology and Aging. In that lecture, BLSA data collected over the past 30 years will be used to examine the long-term stability of self-reported personality; new analyses will present a 7-year longitudinal study of peer ratings--the first such study in the literature. Studies of stability provide the basis for interpreting personality changes that may be indicative of mental or physical disease.

In collaboration with researchers at Duke University Medical Center, LPC investigators have also studied the predictive utility of personality scores gathered from college students. By relating archival MMPI data from undergraduates tested in the mid-1960's to measures of adult personality obtained 24 years later, it is possible to estimate the stability of personality in late adolescence, and thus to determine the probable utility of archival scores for predicting long-term health outcomes. This study showed evidence of both continuity and change between age 20 and age 40, and suggested that the period of the 20's might be a particularly appropriate part of the life cycle in which to conduct research on interventions to alter personality traits.

PSCS researchers have also contributed to advances in our understanding of stress and coping. In a recent issue of Psychological Inquiry, Professor Richard Lazarus presented his model of the stress and coping process, a model that has dominated the field for the past decade. In an invited Commentary, LPC scientists pointed out the need to complement Lazarus' transactional approach with trait measures. Together, enduring dispositions and situationally-responsive coping behaviors can explain adaptational outcomes better than either alone.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00180-05 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Stress, Coping and Personality in Aging Men and Women

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Robert R. McCrae Research Psychologist LPC,NIA

Others: Paul T. Costa, Jr. Chief, LPC LPC,NIA  
Alan B. Zonderman Research Psychologist LPC,NIA

## COOPERATING UNITS (if any)

Longitudinal Studies Branch

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Personality, Stress &amp; Coping

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.6

## PROFESSIONAL:

0.6

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Many previous studies have shown that personality traits are extremely stable in adult males. Two new studies examined stability or change in personality in groups less often studied: women and college students. In the first study, longitudinal and cross-sequential analyses were conducted on the scales of the Guilford-Zimmerman Temperament Survey in a sample of BLSA Women initially aged 23 to 82. Over a seven-year interval there were no significant changes in the mean levels of traits, and stability coefficients were very high and comparable to those seen in men. In the second study, predictive correlations between MMPI content scales measured in college and NEO-PI scales measured 23 years later were compared with concurrent correlations of the same instruments in a BLSA sample. Predictive correlations were qualitatively similar to concurrent correlations, but approximately half as large in magnitude. It appears that about half of the variance in basic dimensions of . . . personality is stable from college age into middle adulthood. Longitudinal research on personality, stress and coping will continue.

EDBP-NIA





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00183-02 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Basic Research in Personality

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Paul T. Costa, Jr. Chief, LPC LPC,NIA

Others: Robert R. McCrae Research Psychologist LPC,NIA  
Alan B. Zonderman Research Psychologist LPC,NIA

## COOPERATING UNITS (if any)

Department of Psychology; Duke University

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Personality, Stress &amp; Coping

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

2.3

## PROFESSIONAL:

2.1

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Personality can be defined in terms of enduring individual differences in emotional, interpersonal, experiential and motivational styles. The five factors of Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness provide a comprehensive taxonomy of personality traits for the description of personality in aging men and women. As part of an ongoing series of studies on these basic dimensions, section investigators examined relations between normal personality traits as measured by the NEO Personality Inventory and measures of motivation and personality disorders. Two measures of Murray's needs--the Edwards Personal Preference Schedule and the Adjective Check List--were correlated with the NEO-PI in both student and adult (BLSA) samples, and showed a meaningful pattern of relations. A second adult sample was used to examine correspondences between personality disorders as measured by the Millon Clinical Multiaxial Inventory and normal personality dimensions. Results suggested that the five-factor model might provide a useful dimensional alternative to the categorical model traditionally used in psychiatric diagnosis.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00184-02 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Psychosocial Predictors of Mental and Physical Health

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Paul T. Costa, Jr.	Chief, LPC	LPC, NIA
Others:	Robert R. McCrae	Research Psychologist	LPC, NIA
	Alan B. Zonderman	Research Psychologist	LPC, NIA
	Chester A. Schmidt	Special Volunteer	FSKMC

## COOPERATING UNITS (if any)

Department of Psychology, University of Maryland Baltimore County  
Department of Psychiatry, Duke University Medical Center

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Personality, Stress &amp; Coping

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

0.6

## OTHER:

0.8

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The relation between normal personality dimensions and indicators of psychopathology was investigated in two samples. Using data from a nationally representative sample followed over 10 years (NHEFS), measures of depression and neuroticism were examined as predictors of psychiatric diagnoses derived from hospitalization records. Proportional hazards analyses showed that depressive symptoms predicted diagnoses of non-depressive disorders as well as depressive disorders, and late as well as early occurrence of the disorder. Both measures of depression showed a pattern of increasing risk with increasing scores, even below the clinical cut-off point. Findings were interpreted to mean that the normal personality dimension of neuroticism predisposes individuals to a wide range of psychiatric problems. In the second study, a measure of normal personality was correlated with two standard measures of psychopathology in two volunteer samples (BLSA and BLSA peers). Correlations suggested that many psychiatric conditions can be described in terms of the five basic dimensions of normal personality, but that personality measures give a broader characterization of the individual than do measures of psychopathology. Efforts to relate basic research on personality to applications in clinical psychology and studies of the relation of personality to physical health will continue.

EDBP-NIA

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00185-02 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Early Markers of Alzheimer's Disease in Longitudinal Participants

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Alan B. Zonderman	Research Psychologist	LPC, NIA
Others:	Paul T. Costa, Jr.	Chief, LPC	LPC, NIA
	Claudia H. Kawas	Staff Neurologist	FSKMC
	Robert R. McCrae	Research Psychologist	LPC, NIA
	Leonard M. Giambra	Research Psychologist	LPC, NIA
	E. Jeffrey Metter	Medical Officer	LSB, NIA
	David L. Arenberg	Guest Researcher	

## COOPERATING UNITS (if any)

Longitudinal Studies Branch, GRC  
Department of Neurology, FSKMC

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Personality, Stress &amp; Coping Section

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

4.8

## PROFESSIONAL:

1.8

## OTHER:

3.0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Participants in the Baltimore Longitudinal Study of Aging aged 60 and older were examined to detect changes in psychological, neurological, and neuropsychological tests related to early signs of Alzheimer's disease. It was hypothesized that impairments in recognition memory after multiple exposures would be sensitive to cognitive impairment that is not characteristic of normal aging. This hypothesis was tested by examining the relationships between recognition memory performance on the Grober-Buschke Cued Selective Reminding procedure and two measures of cognitive status, the Blessed Information-Memory-Concentration Test (BIMC) and the Mini-Mental State Examination (MMSE). Subjects for these analyses were 169 participants who were administered the Army Alpha IQ and verbal fluency tests an average of 23 years prior to the MMSE and BIMC tests. The results showed that . . . recognition memory accounted for 47% and 48% of the variation in the concurrent MMSE and BIMC. Recognition memory also accounted for 33% and 34% of the variation in MMSE and BIMC after removing 24% and 21% of the variation due to the age, education, gender, vocabulary, IQ and fluency tests. These results suggest that deficits in recognition memory performance are independent indicators of mental status, and may provide an age invariant means for detecting cognitive declines.

This project combines Z01 AG 00066-28 LPC and Z01 AG 00064-28 LPC.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00186-01 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Attention, Memory, and Distractibility

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Leonard M. Giambra	Research Psychologist	LPC, NIA
Others:	Alicia Grodsky	Psychologist	LPC, NIA
		DOD 9/90	
	Paul Mullin	IRTA Fellow	LPC, NIA
		DOD 12/89	
	Robin Barr	Expert	BSRP, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.7

## PROFESSIONAL:

1.5

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

One purpose of this research is to examine the influence of aging upon the development and enactment of automatic and effortful attentional processes. We found previously that old adults are unable to attain automatic detection after extensive practice. We are examining the extent to which old adults can go beyond the first level of learning, i.e., "associative" learning, to priority learning which results in automatic detection, a direct and immediate response of the attentional system to the item to be detected. A second purpose of this work is to investigate the relation between age and distractibility. An experimental procedure was developed where subjects are asked to repeat messages presented to one ear (shadowing) while ignoring simultaneous messages in the other ear. Low distractibility is demonstrated by equivalent shadowing performance with and without simultaneous (and different) messages in the other ear. It was previously reported that age and distractibility are directly related. The increase in distractibility with increased age was especially prominent in old adults who had been hospitalized within the prior two years and were on prescription medication. A more precise investigation is now being completed into the moderating effect of health. Also being completed is an investigation in the specific source of the apparent age-related increase in distractibility and reduced ability to control attention. A third goal of this work is to determine the parameters of thought production as well as related mental activity such as insight, attention and sustained attention as phenomena, their interrelations, and their susceptibility to the influence of aging in adulthood. A fourth goal is to examine the relation between memory or forgetting and aging. Six-year longitudinal changes in immediate and short-term delayed memory have been demonstrated. Also demonstrated is the age dependence of forgetting rate during a 24 hour period.

This project combines Z01 AG 00080, 00182, and 00065 LPC.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00187-01 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging Influence on Sustained Attention

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Leonard M. Giambra Research Psychologist LPC,NIA

## COOPERATING UNITS (if any)

Cognitive Sciences Lab, Catholic University, Wash., D.C.

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.6

## PROFESSIONAL:

0.6

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This work attempts to determine the nature of sustained attention and age differences and changes particular to it. Sustained attention is usually examined in a laboratory setting where the salient conditions of sustained attention can be controlled. This year was devoted to collecting data on the influence of extended stimulus inspection time and increased target discriminability on moderating age differences under a high event rate.

Sustained attention as a skill involves both alertness and concentration over long periods of time. This skill plays an important role in both daily living and in the job market place, e.g., jobs requiring inspection. This research provides us with information on how age influences the use and acquisition of that skill as well as how alertness and concentration are susceptible to aging influences.

This project continues Z01 AG 00062-16 LPC.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER  
Z01 AG 00062-16 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging Influences on Sustained Attention and Task-Unrelated Images and Thoughts

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Leonard M. Giambra	Research Psychologist	LPC,NIA
Others:	Alicia Grodsky	Psychologist	LPC,NIA
		DOD 9/90	
	Edwin Rosenberg	Psychologist	LPC,NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

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| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Project Z01 AG 00062-16 LPC is continued by Z01 AG 00187-01 LPC

EDBP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-28 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Problem Solving and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David Arenberg DOD 12/89 LPC,NIA  
(Chief, Cognition Section)

Others: Leonard M. Giambra Research Psychologist LPC,NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Z01 AG 00185-02 LPC Combines: Z01 AG 00064-28 LPC  
Z01 AG 00066-28 LPC

EDBP-NIA



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00065-29 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Verbal Learning and Age

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David Arenberg DOD 12/89 LPC, NIA  
(Chief, Cognition Section)Others: Leonard M. Giambra Research Psychologist LPC, NIA  
Paul Mullin IRTA Fellow LPC, NIA  
DOD 12/89

## COOPERATING UNITS (# any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

Z01 AG 00186-01 LPC combines: Z01 AG 00065-29 LPC  
Z01 AG 00182-3 LPC  
Z01 AG 00080-4 LPC

EDBP-NIA

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STATE OF NEW YORK

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00066-28 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Perceptual Retention and Age

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: David Arenberg

DOD 12/89

LPC, NIA

(Chief, Cognition Section)

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Z01 AG 00185-02 LPC combines: Z01 AG 00066-28 LPC  
Z01 AG 00064-28 LPC

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00080-4 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects on Automatic and Effortful Information Processing

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Leonard M. Giambra Research Psychologist LPC, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Z01 AG 00186-01 LPC combines: Z01 AG 00080-4 LPC  
Z01 AG 00182-3 LPC  
Z01 AG 00065-29 LPC

EDBP-NIA

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00182-3 LPC

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects on Concentration During Information Processing

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Leonard M. Giambra	Research Psychologist	LPC, NIA
Others:	R. Barr	Expert	BSRP, NI
	E.J. Metter	Medical Officer	LSB, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Personality &amp; Cognition

## SECTION

Cognition

## INSTITUTE AND LOCATION

NIH, NIA

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

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| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Z01 AG 00186-01 LPC combines: Z01 AG 00182-3 LPC  
Z01 AG 00080-4 LPC  
Z01 AG 00065-29 LPC

EDBP-NIA

UNITED STATES  
DEPARTMENT OF AGRICULTURE  
OFFICE OF THE SECRETARY

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COOPERATING

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Fiscal Year 1990

Annual Report of the Epidemiology, Demography, and Biometry  
Program

National Institute on Aging

1. Overview of the NIA's Epidemiology,  
Demography, and Biometry Program .....EDBP 1-3
2. Epidemiology Office.....EDBP 4-29
3. Demography and Economics Office .....EDBP 30
4. Biometry Office .....EDBP 31-42

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ANNUAL REPORT OF THE EPIDEMIOLOGY, DEMOGRAPHY, AND BIOMETRY  
PROGRAM

NATIONAL INSTITUTE ON AGING

At the November 30, 1989, Epidemiology, Demography, and Biometry (EDB) Program Ad Hoc Scientific Advisory Committee Meeting, the Piedmont Health Survey of the Elderly (PHSE), one of four Established Populations for Epidemiologic Studies of the Elderly (EPESE) projects, was reviewed in preparation of a contract renewal in FY90. Dr. Dan Blazer, Principal Investigator, outlined research highlights and potential at this North Carolina EPESE site. The Advisory Committee recommended modification of the renewal contract to ensure collection of information which is of particular importance to the study of older black persons and to the study of racial differences among older persons. A Request for Proposal was issued on July 6, 1990, and the Duke proposal, which was received on August 6, 1990, will be reviewed in October. This contract renewal calls for a fifth year telephone contact to begin in January 1991, and a sixth year in-person follow-up contact modified to ensure collection of important racial as well as biomedical and psychosocial information. Five years of surveillance will be conducted for mortality and hospitalizations.

A Request for Proposals (RFP) entitled, "Women's Aging Study" was issued in February for an in-depth study of the causes and course of disability in older women. This study has been specifically designed to focus on disability in older women because women make up a majority of the older population, represent a larger proportion of the total population at each higher age, report higher rates of physical disability than men, spend more years in the disabled state than men, make up a substantially larger proportion of the nursing home population than men, and have greater vulnerability in terms of need for formal and informal care because of their higher rate of widowhood, especially at the oldest ages. Proposals were received June 14, 1990, and the technical review will take place October 15-18, 1990, in Bethesda. We expect a contract to be awarded in the spring of 1991.

Dr. Samuel P. Korper, who served as Acting Associate Director for the EDB Program from July 1989 through June 1990, reported on the Program at the February meeting of the National Advisory Council on Aging. He provided a brief review of the status of the EPESE project and highlighted selected new activities. Dr. William B. Applegate, on behalf of the EDB Program's Ad Hoc Scientific Advisory Committee, commented on the results and recommendations of the November 30, 1989, meeting. He reported that the Committee has been supportive of the Program's unique focus and data collection efforts but suggested that the Program switch from

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hypothesis-generating research to hypothesis-based research, as well as increased emphasis on biologic data collection efforts. Such strategies should continue to solidify collaborative relationships between EDB Program staff and the investigators at the EPESE institutions. The Committee would like to see two or three over-arching themes to more clearly delineate EDB's Program and under each area initiate more hypothesis-based epidemiologic research focused on biologic or performance variables. The final recommendation is that epidemiology issues related to long-term care and possibly health services research issues related to long-term care be further investigated. Four Principal Investigators or Co-Principal Investigators of the EPESE project reported to Council on the status and future directions of research. Dr. Dan Blazer represented the Piedmont Health Survey of the Elderly; Dr. Charles H. Hennekens represented the East Boston Senior Health Project; Dr. Robert B. Wallace represented the Iowa 65+ Rural Health Study; and Dr. Adrian M. Ostfeld, represented the Health and Aging Project in New Haven.

On July 2, 1990, Dr. Richard J. Havlik was detailed to serve as Acting Associate Director of the Epidemiology, Demography, and Biometry Program. Prior to coming to NIA, Dr. Havlik served as Special Assistant for Biomedical Applications in the Office of Planning and Extramural Programs at the National Center for Health Statistics, Centers for Disease Control. His professional interest in epidemiology began in 1968 when he served as a Research Associate in the Epidemiology Branch of the National Heart, Lung, and Blood Institute (NHLBI). From 1980 to 1985 he served as Chief, Clinical and Genetic Epidemiology Section, Epidemiology and Biometry Program, NHLBI. Dr. Havlik has done extensive research in the area of aging and age-related diseases and is a member of a number of professional and scientific societies, including the Gerontological Society of America and the American Epidemiological Society.

The Asia-Pacific Office of the EDB Program was established at Kuakini Hospital in Honolulu on August 2, 1990. The Office Chief (and sole staff member) is Dr. Lon White, formerly Chief of the Epidemiology Office. The principal research project to be conducted through the Asia-Pacific Office is the Honolulu-Asia Aging Study (HAAS). This project involves research on dementia and aging among participants in the Honolulu Heart Program (HHP), a National Heart, Lung, and Blood Institute (NHLBI)-sponsored study of heart disease and stroke, conducted over the past quarter century by a contract with Kuakini Medical Center, Honolulu. NIA funds transferred to the NHLBI during FY90 (Agreement No. Y02-AG-0-0146) were used to supplement the existing contract in support of activities to develop and pretest instruments, and to establish the contract staff and resources necessary to carry out the work outlined in the contract. Senior investigators to be involved in this work have been hired by the

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contractor, and a subcontract for the development of written and video training materials is in place. The following series of meetings and workshops was held in Honolulu this summer: (1) A workshop of consultants to the project to deal with the development of methods and instruments for use in the HAAS and in parallel studies proposed in Tokyo, Osaka, Hiroshima, Taipei, and Seattle. A major focus of the workshop was on continued development of instruments for case identification and neuropsychological assessment and a test for measurement of reaction time using a laptop computer. Both tests are now ready for field testing; (2) A meeting of primary consultants to the HAAS to review the proposed protocol and reach agreement upon a number of important modifications; and (3) A meeting of consultants to be involved in cooperative and comparative neuropathological research to be done in conjunction with the HAAS, where substantial progress was made toward defining methods to be used in autopsies and neuropathological investigations.

The EDB Program continues to provide scientific and financial support to the National Center for Health Statistics (NCHS) Third National Health and Nutrition Examination Survey (NHANES III) (Agreement No. Y02-AG-8-0116-02). NHANES III is a multi-agency collaborative survey designed to estimate the prevalence of diseases and risk factors in some 40,000 Americans. Special efforts are being directed to collection of data from interviews and examinations for the population over 60 and the oldest old. The first data analysis will not occur, however, until after the first 3 years of the projected 6-year data collection period.

An Interagency Agreement was established with NCHS (Agreement No. Y02-AG-0-0154) to support the 1991 Wave of the NHANES I Epidemiologic Follow-up Study (NHEFS). The NHEFS is a longitudinal study which uses as its baseline those adult persons ages 25 to 74 years of age who were examined in the NHANES I. During the period of May to July 1990, the NCHS conducted tracing procedures to keep abreast of the cohort. Upon award of a contract in 1991, the contractor will conduct a 30-minute telephone interview on eligible subjects and death certificates for newly identified deceased subjects will be obtained. These additional years of follow-up will provide important outcome information on mortality and hospitalizations and the added age span of the 1991 wave will provide information on individuals up to approximately 94 years of age.

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## **Epidemiology Office**

Epidemiology Office staff members work with the Associate Director, other EDB Program staff members, other members of the NIA, other investigators at the NIH, Government contractors, the NCHS, and other agencies on a variety of analytical, developmental, methodological, and administrative projects.

Most of the achievements of the Epidemiology Office involved new and continuing analyses of data from established EDB Program projects, including:

1. **Established Populations for Epidemiologic Studies of the Elderly (EPESE)**

The three original community populations comprising the Established Populations for Epidemiologic Studies of the Elderly (EPESE) are located in East Boston, Iowa (Iowa and Washington Counties), and New Haven, Connecticut. Baseline data collection began in December 1981, and annual interviews were conducted either in-person (third and sixth years of follow-up) or by telephone (first, second, fourth and fifth years of follow-up) for 6 years following the baseline. A 5-year extension contract was awarded to each of the three original EPESE cohorts in February 1989. The extensions place major emphasis on data clean-up during the first 2 years of the performance period. The last 3 years of the contract give priority to continued monitoring of mortality through the National Death Index and to monitoring hospital utilization through linkage to Medicare records at the Health Care Financing Administration (HCFA). Arrangements are being made with HCFA to use Medicare Part A (hospitalization) and Part B (outpatient) utilization data to continue monitoring the cohorts for future morbidity and to reconstruct the past morbidity concurrent with the development of the EPESE database on the cohorts.

Contractors submitted final data tapes from the baseline in-person interviews (1982) and the third year follow-up in-person interviews (1985) in December 1989. By December 1990, these three sites will have final data for the first (1983), second (1984), fourth (1986), fifth (1987), and sixth (1988) years of followup. To insure the development of clean and well-documented databases, the Biometry Office staff have furnished standardized documentation to each site as well as editing and error checking programs. These databases will serve as a resource for subsequent sets of data to be archived in the near future.

These sites have been approved by the National Center for Health Statistics (NCHS) for use of this agency's National Death Index to continue monitoring the cohorts for mortality occurring in those years that go beyond the scheduled 6 years

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of followup. As of June 1, 1990, 1,343 of the 3,673 participants in the Iowa cohort had died (37 percent); 1,123 of the 2,812 participants in the Yale cohort had died (40 percent); and 1,552 of the 3,809 participants in the East Boston cohort had died (41 percent).

The Piedmont Health Survey of the Elderly (PHSE) was added as the fourth site of the EPESE project in 1985. In this fourth site, Duke University has established a sample of 4,164 people 65 years old and older, 54 percent of whom are black. This cohort is the only southern EPESE population, constitutes a representative sample of the elderly in five North Carolina counties, and includes both urban and rural participants. The baseline survey for this site began in January of 1986 and was completed in June 1987. The first and second telephone follow-ups of the sample began in January 1987 and 1988. The first telephone follow-up was completed in June 1988 and the second in June 1989. A second in-person follow-up began in January of 1989 and was completed in June 1990. The third telephone follow-up began in January of 1990 and will be concluded in June of 1991. Surveillance of PHSE participants for major endpoints is being conducted currently at the Duke site in a similar manner to that followed by the other three sites, and will continue for the length of the project. Plans include continued surveillance using the National Death Index and HCFA hospitalization data tapes after completing the scheduled 6-year period of direct contact with subjects.

In FY90 the NIA signed an Interagency Agreement with HCFA for supplemental funds for the analysis of prescription and over-the-counter drug data that have been collected at the four EPESE sites. The sites provided detailed analytic plans which were reviewed and approved by the EDB Program and the following analyses are underway:

In Iowa, the second year of followup included a series of questions related to the self-reported occurrence of an adverse drug reaction and what symptoms and circumstances were the result of the reaction. These data will be used to identify the prevalence of drug reactions in this community. Another topic of analysis relates to the long-term use of selected classes of drugs and the outcomes for discontinued use of these drugs.

In New Haven, an extensive amount of data was collected from hospital discharge summaries for approximately 85 percent of the hospitalizations incurred by the members in this cohort at the two major hospitals serving the New Haven community. These data will be used to determine all hospitalizations due to a severe drug reaction over the course of 8 years of hospitalization surveillance. Predisposing characteristics will be



identified as a result of this investigation with an emphasis on the use of digoxin.

In East Boston, patterns of drug use will be examined over time to describe characteristics of users and non-users of the various categories of psychoactive drugs and to determine which factors predict changes in use of these drugs. Preliminary analyses have included determination of the frequency of fractures for each follow-up interview.

In North Carolina, since the data on medication use by blacks differ from that of nonblacks, particular emphasis will be placed on identifying those characteristics which result in the one group differing from the other in prescription and over-the-counter drug use. A study of the concomitants of analgesic drug use will also be conducted.

A tracking system for ongoing analyses provides an effective means to monitor and encourage analyses of EPESE data. Principal Investigators meet with the EDB Program Associate Director and Project Officers on a quarterly basis to coordinate this process.

## 2. Women's Aging Study (WAS)

This project was developed with the goal of using a community-based epidemiologic study to examine a number of important issues related to the health and functioning of older women in America. Compared to past EDBP research, it is conceived as more detailed, more biomedically oriented research to be done on a smaller, more intensively studied community-dwelling sample of older women, with sampling designed to produce a study cohort enriched in persons with and/or at increased risk of developing disabilities and functional impairments. Objectives of the WAS will include identifying patterns of progression or resolution of states of impairment and disability, patterns of health care utilization associated with specific impairments and disabilities, and factors influencing/ predicting such outcomes and consequences. The RFP was issued in February 1990; proposals were received June 14; and a technical review will take place October 15-18, 1990. We expect a contract to be awarded in the spring of 1991.



3. Development of research projects in the Pacific and Asia;  
establishment of an Asia-Pacific Office.

The Asia-Pacific Office of the EDBP was established at Kuakini Hospital in Honolulu on August 2, 1990. The Office will have three main functions: (1) to conduct epidemiologic research related to aging and dementia in the Asia-Pacific area (largely through the Honolulu-Asia Aging Study, HAAS), (2) to assist in the coordination of other Institute and Program interests in the Pacific and Asia, and (3) to assist in the training of developing investigators in Hawaii interested in the epidemiologic aspects of aging, and to provide guidance and advice to local students and faculty wishing to develop research careers in this area of research. The Office Chief (and sole staff member) is Dr. White, formerly Chief of the Epidemiology Office.

(a) The Honolulu-Asia Aging Study

The principal research project to be conducted through the Asia-Pacific Office is the Honolulu-Asia Aging Study (HAAS). This project, planned over the past 3 years (see previous source books and annual reports), involves research on dementia and aging among participants in the Honolulu Heart Program (HHP), an NHLBI-sponsored study of heart disease and stroke, conducted over the past quarter century by a contract with Kuakini Medical Center, Honolulu. Dr. White is the Director, HAAS; Dr. Dwayne Reed (an NHLBI staff member) is the Director, HHP; Dr. J. D. Curb is the Principal Investigator, HHP.

The HHP is a longitudinal epidemiologic study designed to identify factors influencing the development of cardiovascular diseases. The study began in 1965 with the examination of 8,006 Japanese-American men living in Hawaii and born 1900 through 1919. As a result of several examination cycles and an on-going surveillance for cardiovascular illness endpoints, a great deal of information has been collected and is currently available for computerized analysis. Through an Inter-institute Agreement with the NHLBI, the NIA will supplement the NHLBI contract to allow research on dementia and aging in study participants. The specific research goals of the NIA-supported contract supplement will be to:

- identify and classify all prevalent cases of dementia among HHP participants during the course of the upcoming cycle of examinations (1990-92);
- identify and classify all incident cases of dementia developing over a period of two years, based upon re-survey of the cohort and re-evaluation of a selected sample during 1992-1994;

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- determine the clinical course and survival of all study participants evaluated and classified as having a dementing illness;
- estimate age-specific prevalence and incidence rates for Alzheimer's Disease, multi-infarct dementia, and other types of dementing illnesses in this cohort;
- estimate age-specific prevalence rates for cognitive and physical impairment among wives of HHP participants;
- using previously collected data, investigate and identify risk factors for vascular dementia and Alzheimer's Disease, with a specific focus on factors associated with acculturation; this will involve an effort to separate genetic from environmental factors influencing the development of dementia,
- investigate and identify early signs and symptoms that herald the imminent development of dementia,
- conduct clinical and neuropathological research to (a) evaluate the accuracy of clinical diagnoses, (b) to investigate factors influencing development of the neuropathologic changes of Alzheimer's disease, and (c) to investigate factors influencing the clinical expression of these changes as dementia,
- collect, store, and utilize tissue and body fluid samples for research (as yet undefined) related to the pathogenesis of dementia and other illness of aging.

The upcoming examination of HHP participants is currently scheduled to begin on March 1, 1991. A 20 percent sample (including all participants scoring in the bottom 10 percent on a test of cognitive functioning) will receive a follow-up evaluation 2-12 weeks after their baseline examinations in order to identify and establish diagnoses for cases of dementia.

Agreements have been reached with the Department of Veterans Affairs (DVA) and with the National Center for Nursing Research (NCNR) for a DVA neuroscientist and a nurse researcher to join the project and to work as HAAS researchers in January 1991.

NIA funds transferred to the NHLBI during FY90 were used to supplement the existing contract in support of activities to develop and pretest instruments, and to establish the contract staff and resources necessary to carry out the work outlined above. Senior investigators to be involved in this work have been hired by the contractor, and a subcontract for the development of written and video training materials is in place.



On July 10 and 11 a workshop of consultants to the project was held in Honolulu dealing with the development of methods and instruments for use in the HAAS and in parallel studies proposed in Tokyo, Osaka, Hiroshima, Taipei, and Seattle. The workshop was chaired by Dr. White. A major focus of the workshop was on continued development of instruments for case identification and neuropsychological assessment (currently being referred to as the Cognitive Assessment and Screening Instrument, CASI, developed by Dr. Evelyn Teng in collaboration with Dr. White, Dr. Kazuo Hasegawa, Dr. Eric Larson, and others) and a test for measurement of reaction time using a laptop computer. Both tests are now ready for field testing.

On July 12 a meeting of primary consultants to the HAAS was held in Honolulu. This group consisted of Drs. Eric Larson, William Marksbery, and Evelyn Teng. Others attending this meeting included Dr. White, Dr. Reed (Director, HHP), Dr. Curb (PI, HHP), and many of the staff of the HHP contract. The proposed protocol for the HAAS was reviewed and a number of important modifications agreed upon.

On July 13 a meeting of consultants to be involved in cooperative, comparative neuropathological research to be done in conjunction with the HAAS was held in Honolulu. This group included Dr. Marksbery, Dr. John Hardman (U. Hawaii), Dr. Mark Sumi (U. Washington, Seattle), and Dr. Jun Ogata (National Cardiovascular Center, Osaka). Very substantial progress was made toward defining methods to be used in autopsies and neuropathological investigations.

(b) Activities of the Asia-Pacific Office related to other Institute and Program research interests in Asia and the Pacific.

The HAAS was designed in response to reported differences in occurrence of Alzheimer's disease and Multi-infarct Dementia between Japanese (as well as Chinese) and European-ancestry populations. Cooperative relationships have been established with investigators in Japan, Taiwan and Seattle with the objective of conducting parallel studies in Asian-ancestry populations at 3 to 6 sites using similar methodologies to ensure that research results will be comparable. It has been understood from the outset that the EDBP, NIA would not provide funds in support of data collection and analysis at sites other than Honolulu. Funding for the parallel studies will be accomplished independently for each site. However, NIA funds have been used on two occasions to convene the key personnel to be involved in these studies. More importantly, preliminary planning for the HAAS budget had included a modest level of funding to support future cooperative activities involved in methods development, training, quality control, and cooperative analysis.



During FY90 the NHLBI indicated that it wished to limit activities supported through the supplement to the NHLBI HHP contract to those directly related to research on HHP participants, and specifically requested that the supplement not support international cooperative research activities. This development implies that these activities must be supported through some other mechanism. Mechanisms under consideration include establishing an independent contract to support such activities, liberal use of professional services contracts, or fund transfers to (or other type of working agreement with) another agency wishing to participate in project.

(c) Activities of the Asia-Pacific Office related to training and to assisting developing researchers in Hawaii.

To facilitate this objective our preliminary plan has been to establish an administrative entity within the University of Hawaii School of Medicine to be (tentatively) designated the Asia-Pacific Office for Research on Aging (APORA). The APORA will be staffed by three (or more) federal researchers as adjunct faculty members (Dr. White; an as yet unselected DVA neuroscientist; an as yet unselected NCNR nurse researcher) and possibly by local scientists. Through the APORA, and through collaboration with Dr. White or other NIA (EDBP) researchers, local Hawaiian students and faculty will be provided controlled access to existing EDBP data sets for the purpose of conducting defined analyses. As indicated by the following points, the APORA is at a very rudimentary stage of development: (1) since the APORA has not yet been created as an entity within the School of Medicine, it currently exists only as a concept; (2) neither the DVA neuroscientist nor the NCNR researcher have yet been identified or fully committed; (3) the University is currently unable to contribute any space or other resources to make the APORA more than an administrative entity. Until the APORA is a more fully defined entity, objective #3 of the Asia-Pacific Office will be addressed by the informal provision of assistance, advice, and training to local researchers by Dr. White as requested and as time and resources allow.

#### 4. NHANES III: Health of Older Americans (Baseline Survey)

NHANES III is planned as a multi-agency collaborative survey designed to estimate the prevalence of diseases and risk factors in some 40,000 Americans. Special efforts are being directed to collection of data from interviews and examinations for the population over age 60 and the oldest-old. NCHS will carefully monitor survey operations, review response rates, review quality control materials and develop and institute corrective steps when necessary, and review preliminary distribution of results.



5. Analytic and developmental accomplishments by Epidemiology Office staff.

Dr. Jack Guralnik collaborated with Dr. Edward Schneider, Dean, Andrus School of Gerontology, University of Southern California, on projections of how the future growth of the older population will affect cases of chronic debilitating disease and health care expenditures. At the time their paper was published Drs. Guralnik and Schneider were asked to participate in a press conference to announce the results at the U.S. Capitol. Also at the press conference to underscore the need for increased research in aging were Joseph Califano, HEW Secretary, 1977-1979, National Spokesperson, Project Independence for Older Americans and Senator Tom Hartkin of Iowa (Chairman, Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies). Dr. Guralnik appeared on ABC television to answer questions about the study, which received widespread attention in the press around the country. Dr. Guralnik presented the findings of the paper to the Board of Directors of the Alliance for Aging Research.

Dr. Guralnik serves as an NIA representative to the working group of the MacArthur Studies of Successful Aging in Humans. This group was organized for the purposes of analyzing and publishing results from the studies being conducted at EPESE sites in Durham, NC; East Boston, MA; and New Haven, CT. Dr. Guralnik attended the first meeting of the working group on March 5, 1990, the purpose of which was to develop understandings on how all parties that contributed to the MacArthur research, including EDBP, might benefit from the rich data base generated by this study.

Dr. Guralnik was invited to the University of Michigan, where he was asked to consult with researchers at the Institute of Gerontology, the Institute for Social Research, and the School of Medicine. He presented two formal talks during his visit.

Dr. Guralnik was asked to participate in a small conference on the compression of morbidity at Asilomar in Monterrey, California sponsored by the Kaiser Research Foundation.

Dr. Lon White traveled to The Netherlands and to Belgium in December to participate as a referee for the thesis defense of Dorly Deeg (she received her Ph.D. from Erasmus University), which involved research conducted in part at the EDB Program, NIA. While in Europe, Dr. White consulted with researchers involved in research on dementia and aging at The Hague, Amsterdam, Rotterdam, and Belgium. This trip resulted in the establishment of relationships, an exchange of information on methods, and an enhanced communication that will improve the comparability of results generated by our different research studies.

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Dr. White traveled to Hiroshima, Japan in March at the invitation of the Radiation Effects Research Foundation (RERF) to participate in a workshop on Aging. As a result of this workshop, the RERF has extended its plans to include research on aging and dementia in its future research agenda, specifically including a study on dementia to be done in parallel with the EDB Program's Honolulu-Asia Aging Study.

Dr. White traveled to Stockbridge, Massachusetts in May, at the invitation of the Environmental Health Institute (affiliated with the Berkshire Health Systems) to participate in a workshop on environmental factors in neurodegenerative diseases. This workshop focused upon the potential role of natural and man-made neurotoxins in the pathogenesis of chronic, degenerative neurological diseases and behavioral abnormalities. Special attention was given to the possible etiologic roles of excitotoxins, aluminum, botanical neurotoxins (as of the cycad family) and exposure in combination or at times of special susceptibility.

In June, Drs. White and Korper met with several researchers at Boston University's School of Medicine to discuss possible approaches to the study of dementia in Boston, with an emphasis on special opportunities related to research in older black men and women.

During the first half of FY90 Dr. White continued in his role as the Chair of the NIH Epidemiology Committee. One of the more important of its monthly meetings concerned the public release of datasets generated in the course of contract-funded epidemiologic research, with special emphasis on issues of privacy, and differences in mechanisms and regulations concerning release of datasets generated by grant versus contract-supported research. In July Dr. White convened a special panel of distinguished Federal epidemiologists to identify a new committee chairperson and/or to establish a mechanism to maintain the activities of the Committee following his assignment to Honolulu.

## 6. Talks and Presentations

Dr. White was an invited participant at the Fourth International Congress of Psychogeriatrics, held in Tokyo in October. He presented a paper on cross-cultural research on dementia.

Guralnik JM, LaCroix AZ, Curb JD, Berkman L, Evans D, Wallace R: Maintaining mobility in late life: the role of demographic factors and chronic conditions. Presented at the 117th Annual Meeting of the American Public Health Association, Chicago, IL, October 1989.

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Guralnik JM: Evaluating functional status through performance measures of physical functioning. Presented at the Federal Forum on Aging Related Statistics, Bethesda, MD, November 1989.

Guralnik JM: The epidemiology of disability and the associated needs for care. Presented in the symposium "Physical Frailty, A Treatable Cause of Dependence in Old Age" at the 42nd Annual Scientific Meeting of the Gerontologic Society of America, Minneapolis, MN, November 1989.

Guralnik JM: An epidemiologic perspective on research on health promotion and disease prevention at older ages. Presented at the 42nd Annual Scientific Meeting of the Gerontologic Society of America, Minneapolis, MN, November 1989.

Guralnik JM: Assessing physical functioning in cross-cultural aging studies. Presented at the 42nd Annual Scientific Meeting of the Gerontologic Society of America, Minneapolis, MN, November 1989.

White LR: Cross-cultural research on dementia. Presented at the 42nd Annual Scientific Meeting of the Gerontologic Society of America, Minneapolis, MN, November 1989.

Guralnik JM: Has increased longevity increased the potential worklife. Presented at the 2nd Annual Conference of the National Academy of Social Insurance, Washington, D.C., January 1990.

Guralnik JM: The maintenance of mobility: prospective evidence from three populations. Presented at the Institute of Gerontology, University of Michigan, March 1990.

Guralnik JM: Research and clinical applications of performance measures of physical functioning. Presented at the School of Medicine, University of Michigan, March 1990.

Guralnik JM: Prospects for the compression of morbidity: A scenario based on projections of disability prior to death. Presented at the Kaiser Foundation Research Institute conference "A Research Agenda on the Compression of Morbidity," Monterey, CA, March 1990.

Wienpahl, J: Body mass index, alcohol use, and smoking in relation to hip fracture in older populations. Presented at the Annual Meeting of the Society for Epidemiologic Research in Snowbird, Utah, June 1990.



## 7. Research Highlights for Fiscal Year 1990

- An overview of available information from the NHEFS on cerebrovascular disease revealed an increasing prevalence of disease with age. Cases were identified by careful review of questionnaire, hospital and death certificate diagnoses of cases which occurred during the approximately 10-year period between the NHANES baseline and the 1982-84 follow-up. Incidence over the same period also showed dramatic increases with age. Survival curves demonstrated an immediate mortality of 35-40 percent following first diagnosis of a thromboembolic stroke and 75-80 percent following a hemorrhagic stroke. For thromboembolic stroke statistically significant risk factors included age, male sex, systolic blood pressure in excess of 166 mmHg, hemoglobin in excess of 15.7 g/dl and a prior history of heart disease. For hemorrhagic stroke risk factors included age, hemoglobin in excess of 15.8 g/dl and prior history of diabetes. (White et al., Cerebrovascular disease, in Cornoni-Huntley, Huntley and Feldman, eds. Health Status and Well-Being of the Elderly, Oxford University Press, 1990, pp. 115-135.)

- Comorbidity was studied in the National Health Interview Survey Supplement on Aging (SOA). Data from this study showed that a higher percentage of women than men age 60 and older experienced two or more of the nine common chronic conditions reported in the SOA. Linear increases were observed in the number of persons having difficulty or needing help with activities of daily living as the number of chronic conditions increased. Also, with increasing age a decrease was found in the proportion of persons experiencing none of the nine conditions. (Guralnik, et al. Comorbidity of chronic conditions and disability among older persons - U.S. Morbidity and Mortality Weekly Report, 1990;38(46):788-91.)

- Baseline neuropsychological function was assessed in 2,123 Framingham Heart Study participants and was related to mortality over an 8- to 10-year follow-up period. During that time, 573 persons died. Using Cox proportional hazards models, the authors showed poor cognitive function to be consistently associated with an increased risk of death. This association persisted after adjustment for the confounding effects of age, education, and illness. Subjects scoring below the 26th percentile of performance were at increased risk of mortality compared with high scorers (the relative risk was 1.3 for the 11th percentile-25th percentile and 1.7 for the 1st percentile-10th percentile). (Liu, LaCroix, White, Kittner, and Wolf. Cognitive impairment and mortality: a study of possible confounders. Am J Epidemiol, 1990;132:136-43.)



• Angina pectoris is a manifestation of coronary heart disease, yet little is known from clinical or epidemiologic studies about its prognosis in older populations. We investigated the relation of uncomplicated angina symptoms to risk of coronary heart disease mortality within 3 years in a prospective study of 8,359 people aged 65 and older residing in the three EPESE communities (East Boston, MA; New Haven, CT; Iowa and Washington counties in rural Iowa). From baseline (1981-1983) to the third year of follow-up (1984-1986), there were 245 deaths from coronary heart disease. Three classifications of chest pain were defined using the Rose Questionnaire: nonexertional chest pain, chest pain on exertion (including angina), and angina. Exertional chest pain was a strong, independent predictor of coronary heart disease death for older men and women. There were no differences in the prognostic implications of this symptom between the sexes; the relative risks being 2.4 in men and 2.7 in women. The risk of coronary heart disease mortality for those reporting chest pain on exertion was at least as high as that for participants whose symptoms met the Rose Questionnaire criteria for angina. The association between exertional chest pain and coronary heart disease mortality was independent of other coronary risk factors. The relation was specific for deaths from coronary heart disease, as there was no association between exertional chest pain and noncoronary causes of death. Chest pain on exertion conveys important prognostic information about risk of coronary death in older populations, regardless of gender. (LaCroix, Guralnik, Curb, Wallace, Ostfeld, and Hennekens. Chest pain and coronary heart disease mortality among older men and women in three communities. Circulation 1990;81:437-446.)

• Thiazide diuretic agents lower the urinary excretion of calcium. Their use has been associated with increased bone density, but their role in preventing hip fracture has not been established. A prospective study of the effect of thiazide diuretic agents on the incidence of hip fracture was conducted among 9,518 men and women 65 years of age or older residing in three EPESE communities in East Boston, New Haven, and Iowa and Washington counties in rural Iowa. At baseline, 24 to 30 percent of the subjects were thiazide users. In the subsequent 4 years, 242 subjects had hip fractures. The incidence rates of hip fracture were lower among thiazide users than nonusers in each community; the Mantel-Haenszel relative risk of hip fracture, adjusted for community and age, was 0.63. The protective effect of the use of thiazides was independent of sex, age, impaired mobility, body-mass index, and current and former smoking status; the multivariate adjusted relative risk of hip fracture was 0.68. Furthermore, the protective effect was specific to thiazide diuretic agents, since there was no association between the use of antihypertensive medications other than thiazides and the risk of hip fracture. These





prospective data suggest that in older men and women the use of thiazide diuretic agents is associated with a reduction of approximately one third in the risk of hip fracture. LaCroix, Wienpahl, White, Wallace, Scherr, George, Cornoni-Huntley, and Ostfeld. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med 1990;322:286-90.

- The rapid growth of the oldest age groups will have a major impact on future health care cost. Current U.S. Census Bureau projections were used for the growth of our oldest age groups to project future costs for Medicare, nursing homes, dementia, and hip fractures. Without major changes in the health of our older population, these health care costs will escalate enormously, in large part as a result of the projected growth of the "oldest old," those aged 85 years and above. Medicare costs for the oldest old may increase sixfold by the year 2040 (in constant 1987 dollars). It is unlikely that these projected increases in health care costs will be restrained solely by cost-containment strategies. Successful containment of these health care costs will be related to our ability to prevent and/or cure those age-dependent diseases and disorders that will produce the greatest needs for long-term care. (Schneider, Guralnik. The aging of America: Impact on health care costs. JAMA 1990; 263:2335-40.)

- The relation of longitudinally measured blood pressure to cognitive performance in the absence of clinically diagnosed cerebrovascular disease was investigated in the Framingham Study. In 1976-1978, neuropsychologic testing was administered to 1993 participants aged 55-89 years. Performance on an education-adjusted composite of these tests was examined in relation to measures of chronicity of hypertension as well as the average systolic and average diastolic blood pressure. All analyses were stratified by antihypertensive medication use during the 2 years prior to cognitive testing and adjusted for age, sex, occupation, alcohol consumption, and participation rate in prior examination cycles. Among subjects on drug therapy for hypertension, there was no association between cognitive performance and longitudinally measured blood pressure. The proportion of cycles in which hypertension was present and average systolic and diastolic blood pressure had a significant inverse relation with cognitive performance only in the group not on antihypertensive drug therapy. However, among subjects on antihypertensive medication at earlier cycles, there was a highly significant graded relation between cognitive impairment and the probability of being off medication at the time of testing. These results suggest that hypertension-related subclinical vascular disease is not an important cause of cognitive impairment in the elderly. Cognitive impairment may, however, be associated with a



reduced adherence to drug treatment regimens. (Farmer, et al. Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: The Framingham Study. J Clin Epidemiol, 43(5):475-80, 1990.)

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## CONTRACT

Name and Number: Yale University (N01-AG-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$582,708

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to study representative community-dwelling populations. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: Continued surveillance during a 5-year period (1989-93) will be based on the use of the National Death Index for mortality and the Health Care Financing Administration's Medicare data for morbidity. Yale University has also negotiated a subcontract with the State of Connecticut to continue nursing home admission surveillance based on the use of the statewide Nursing Home Admissions Registry. Data from the state's Division of Motor Vehicles will be used to augment the driving practices data collected in a seventh year of follow-up in 1989 in this site.

Major Findings: The ability of global self-evaluations of health to predict survival in follow-up studies was tested in both the Yale and Iowa EPESE cohorts. These data were used to investigate the association between 1982 self-evaluated global health status and survivorship from 1982 to 1986. Despite extensive controls for physical health status in the form of measures of disabilities and chronic conditions, sociodemographic characteristics, and health risk behaviors at the beginning of the follow-up period, and the use of analytic techniques which take into account the stratified sample design of the New Haven data, poor self-perceptions of health significantly increase the risk of mortality. Adjusted odds ratios for the extreme categories for New Haven men and women were 5.33 and 2.99,

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respectively; for Iowa men and women they were 4.84 and 3.16. Respondents reporting "fair" and "good" health also showed elevated risks of mortality in dose-response fashion. Self-perceptions of health status appear to be a factor of unique prospective significance in mortality studies (ref. 1).

Grade of membership (GOM) representations were used to characterize and compare the health status of this cohort. Ideal profiles based on functional disabilities, chronic disease, and selected biomedical and behavioral risk factors were constructed empirically. Each individual in the sample was represented by a set of GOM scores, interpreted as degrees of similarity of his or her health record to each of the profiles. Four profiles form GOM analyses: healthy elderly, elderly with cognitive impairment, elderly with impairment in mobility function and physical performance and with selected chronic conditions, and elderly with major limitations in activities of daily living and multiple chronic conditions. Although elderly blacks and whites generally have similar configurations of profiles, there were important differences, especially when chronic conditions were related to specific types of functional impairments. Questions about and claims for black/white mortality crossovers at older ages, usually addressed with aggregate data, were examined conditional on GOM scores that correspond to diverse combinations of disabilities (or lack thereof) together with housing characteristics of cohort member (e.g., whether they live in public housing for the elderly or in owned or rented housing in the community) (ref. 2).

### Publications

1. Idler EL, Kasl SV, and Lemke JH. Self-evaluated health and mortality among the elderly in New Haven, Connecticut, and Iowa and Washington counties, Iowa, 1982-1986. Am J Epidemiol 1990;131:91-103.
2. Berkman LF, Singer B, and Manton K. Black/White differences in health status and mortality among the elderly. Demography. 1989;26:661-678.

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## CONTRACT

Name and Number: University of Iowa (N01-AG-0-2106)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$104,087

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to study representative community-dwelling populations. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: Continued surveillance during a 5-year period (1989-93) will be based on the use of the National Death Index for mortality and the Health Care Financing Administration's Medicare data for morbidity. A seventh year of follow-up interviews was conducted with additional information obtained on driving practices. This newly created database was linked with the Iowa Driver's License Tape and matches were sent to the Iowa Department of Transportation to run against their current history file. Nursing home admission and discharge dates were confirmed and updated with the Follow-Up VII interview survey.

Major Findings: Sociodemographic, health, and psychobehavioral correlates of anticipated and actual relocation were examined. Intent to move was associated with higher levels of depressive symptoms. Of those responding, 4.8 percent moved between the baseline and 1-year follow-up interviews. Disproportionally high numbers of women, persons over 84 years of age, those who lived alone, persons with lower incomes, and the less educated made noninstitutional moves. Actual noninstitutional relocation was associated with poorer physical functional status, poorer self-perceived health status, higher levels of depressive symptomatology and anxiety, and poorer life satisfaction at baseline. Death of spouse, marriage of offspring, and having

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someone move in with the respondent were associated with noninstitutional relocation, but retirement was not (ref. 1).

First analysis of the nursing home portion of these data and first investigation of associations between drug use and health outcome in this cohort of nursing home residents does not support an association between use of psychotropic drugs and 3-year mortality (ref. 2).

The relationship between cognitive functioning and self-reported sensory functioning was investigated. Obtained were two performance measures and two subjective measures of cognitive function. Poorer self-rated vision was associated with poorer scores on the performance measures; poorer self-rated hearing was associated with poorer scores on the performance and subjective measures. Adjustment for age, educational attainment, physical health status, and depressive symptoms accounted for most of the relationships between the performance measures of cognition and vision and hearing function and the subjective measures of cognition and vision function. However, subjective measures of cognitive function remained related to hearing after adjustment. Thus clear evidence of a relationship between sensory function and cognitive performance in a population of noninstitutionalized elderly persons was not found (ref. 3).

Preparation for retirement in the rural elderly and the relationship between that preparation and retirement satisfaction was investigated. A number of anticipatory socialization for retirement mechanisms were investigated including planning for retirement, preretirement education, gradual versus immediate retirement, discussion of retirement with others, and exposure to written information and mass media programs about retirement. Planning for retirement, reading about retirement, and exposure to radio or television programs about retirement were significant correlates of retirement satisfaction for both sexes. Gradual retirement was a significant correlate of retirement satisfaction for males only. After health, planning for retirement was the second strongest predictor of retirement satisfaction for males (ref. 4).

An investigation was conducted of the quantity and quality of intergenerational and sibling relationships in retired rural men and women as well as personal background factors associated with quantity and quality of kinship relations in those retired men and women. As evidenced by proximity, frequency of contact, receipt of aid, affectional closeness, and value consensus with kin, retired rural elderly appear well integrated into kinship networks, with females advantaged over males. Kinship relationships are affected by health, financial status, marital status, and age. Implications for practitioners and program planners were discussed (ref. 5).

When data on health status were used to determine the ratio of persons with activities of daily living (ADL) dependencies living



in the community to those in institutions, results indicated that the "community/institutional dependency ratio" is about 1 to 1 for these counties, which is about half the ratio representing conventional wisdom. In addition, it was found that the level of ADL dependency can serve alone as an almost certain predictor of institutionalization for some elderly. For others, ADL dependency is only one factor. The likely variability of the community/institutional dependency ratios across different geographic areas has implications for government funding of home health care, for long-term care insurance, and for eliminating excess demand (ref. 6).

#### Publications

1. Colsher PL and Wallace RB. Health and social antecedents of relocation in rural elderly persons. J Gerontol: Social Sciences, 1990;45:S32-S38.
2. Chrischilles EA, Nduaguba M, Wallace RB, and Semla TP. Psychotropic drug use and health outcomes in nursing homes. Pharmacoepidemiology: Volume 1, ed. SA Edlavitch, Lewis Publishers, 1989.
3. Colsher PL and Wallace RB. Are hearing and visual dysfunction associated with cognitive impairment? A population-based approach. J Appl Gerontol 1990;9:91-105.
4. Dorfman LT. Retirement preparation and retirement satisfaction in the rural elderly. J Appl Gerontol 1989;8:432-50.
5. Dorfman LT and Mertens C. Kinship relations in retired rural men and women. Family Relations 1990;39:166-73.
6. Nyman JA, Cyphert ST, Russell DW, and Wallace RB. The ratio of impaired elderly in the community to those in nursing homes in two rural iowa counties. Medical Care 1990;27:920-27.

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## CONTRACT

Name and Number: Peter Bent Brigham Hospital (N01-AG-0-2107)

Title: Established Populations for the Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$332,591

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged.

Methods Employed: The project includes cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population is included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to study representative community-dwelling populations. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: Continued surveillance during a 5-year period (1989-93) will be based on the use of the National Death Index for mortality and the Health Care Financing Administration's Medicare data for morbidity.

Major Findings: Data from this cohort were used to describe the characteristics of headache in the elderly. Subjects were asked whether they experienced headache in the past year, the frequency and severity of their headaches, and whether they experienced three symptoms of migraine: unilaterality, nausea or vomiting, an aura preceding the headache. Prevalence of headache in those aged more than 65 years declined with age in both men and women; women had a higher prevalence in each age group. The same was true for frequent, severe, and migrainous headache. Age- and sex-adjusted correlations of headache were examined with several medical and social factors. Prevalence of any headache was strongly associated with joint pain, depression, bereavement, waking during the night, use of eyeglasses, symptoms of temporomandibular joint dysfunction, and self-assessment of health. Similar variables were associated with frequency, severity, and migrainous symptoms, and thus could not be distinguished among these various types (ref. 1).

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Clinically diagnosed Alzheimer's disease (AD) and other dementing illnesses were assessed in a stratified sample of 467 persons who underwent neurological, neuropsychological, and laboratory examination. Prevalence rates of AD were calculated for the community population from the sample undergoing clinical evaluation. Of those over the age of 65 years, an estimated 10.3 percent had probable AD. This prevalence rate was strongly associated with age. Of those 65 to 74 years old, 3.0 percent had probable AD, compared with 18.7 percent of those 75 to 84 years old and 47.2 percent of those over 85 years. Other dementing conditions were uncommon. Of community residents with moderate or severe cognitive impairment, 84.1 percent had clinically diagnosed AD as the only probable diagnosis. These data suggest that clinically diagnosed AD is a common condition and that its public health impact will continue to increase with increasing longevity of the population (ref. 2).

Investigators reported the level of performance on several activities of daily living and physical function scales for a population of elderly persons, and the relationship between self-reported limitations or difficulties and future use of home care services, as well as mortality within this community population (ref. 3).

#### Publications

1. Cook NR, Evans DA, Funkenstein HH, Scherr PA, Ostfeld AM, Taylor JO, and Hennekens CH. Correlates of headache in a population-based cohort of elderly. Arch Neurol. 1989;46:1338-1344.
2. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, and Taylor JO. Prevalence of Alzheimer's disease in a community population of older persons; higher than previously reported. JAMA 1989;262:2551-2556.
3. Scherr PA, Branch LG, Wetle T, Evans DA, and Taylor JO. Physical function as a measure of health status in the East Boston elderly. In: Lerner DJ and Loew RM eds. Elders at risk. Boston, MA: Massachusetts Health Data Consortium 1989:9-21.



## CONTRACT

Name and Number: Duke University Medical Center (N01-AG-4-2110)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: September 30, 1984

Current Annual Level: \$1,044,243

Objectives: The purpose of this project is to conduct epidemiologic investigations in an elderly population, 65 years of age and older, selected from both urban and rural locations and of which at least 50 percent is black.

Methods Employed: Descriptive and analytical epidemiologic studies of existing problems and surveillance of newly developing problems all with an emphasis upon future intervention and prevention have been conducted. Investigators conducted cross-sectional and prospective studies as well as more detailed problem-related studies in a carefully defined and accessible population using standard field and analytical techniques.

Significance to Biomedical Research: The NIA began funding three population studies of the elderly to determine the influences of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the elderly. These studies, however, were not fully representative of the U.S. elderly; specifically, they did not include a significant proportion of blacks. It is well known that distributions of certain risk factors and diseases differ between U.S. blacks and other racial groups. Therefore, the purpose of this contract is to conduct epidemiologic investigations in an elderly population of which at least 50 percent is black in order to develop new knowledge concerning the medical and social factors in health and diseases of the aging black population. In addition, both black and white subgroups in the study exhibit an excellent distribution on indicators of socioeconomic status, and participants have been selected from both urban and rural locations. Therefore, urban-rural, as well as black-white comparisons can be made.

Proposed Course: An extension to the contract is planned for a fifth year telephone follow-up contact and a sixth year in-person follow-up contact, followed by 5 years of surveillance. This data collection format is consistent with the design of the initial three EPESE sites. The 5 years of surveillance shall monitor the population for mortality and health care utilization using surveillance systems involving no or minimal direct contact with study subjects.

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### Publications

Cornoni-Huntley J, Blazer DG, Lafferty ME, et. al. (Eds.):  
Established Populations for Epidemiologic Studies of the Elderly,  
Volume II, Resource Data Book NIH Publ. No. 90-495. U.S.  
Government Printing Office, Washington, D.C., 1990.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 07040 01 EDBP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Honolulu Aging Study

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Lon R. White, M.D., M.P.H., Chief, Asia-Pacific Office, EDBP  
Robert Garrison, M.S., Chief, Field Studies Branch, EBP, NHLBI

## COOPERATING UNITS (if any)

National Heart Lung and Blood Institute (NHLBI)

## LAB/BRANCH

Epidemiology Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

.9

## PROFESSIONAL:

.85

## OTHER:

.05

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The National Institute on Aging (NIA) will supplement a research project (the Honolulu Heart Program) sponsored by the NHLBI and supported through an NHLBI contract with Kuakini Medical Center in Honolulu, Hawaii, to allow for research on aging and dementia among study participants. The Honolulu Heart Program is a prospective study of cardiovascular diseases of American men of Japanese ancestry born from 1900 to 1919 and living on the island of Oahu in 1965. This study will focus on aging, with the emphasis on Alzheimer's disease and multi-infarct dementia. Approximately 5,200 men and 1,000 women will be contacted over a 2-year period. The men will be aged 70 to 90 and the women 50 to 95. Data collection method and procedures involve examination and interview of individual participants, including blood drawing and testing.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 07030 02 EDBP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NHANES III: Health of Older Persons (Baseline Survey)

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D., Chief, Biometry Office, EDBP, NIA  
Robert Murphy, Division of Health Examination Statistics, NCHS

## COOPERATING UNITS (if any)

National Center for Health Statistics

## LAB/BRANCH

Biometry Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

.05

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

NHANES III is planned as a multi-agency collaborative survey designed to estimate the prevalence of diseases and risk factors in some 40,000 Americans. Special efforts are being directed to collection of data from interviews and examinations for the population over age 60 and the oldest-old.

NCHS will carefully monitor survey operations, review response rates, review quality control materials and develop and institute corrective steps when necessary, and review preliminary distribution of results.

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## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01AG 07050 01 EDBP

## PERIOD COVERED

October 1, 1989 to September 30, 1990

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NHANES I Epidemiologic Followup Study (NHEFS)

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D., Chief, Biometry Office, EDBP, NIA  
Madelyn Lane, Office of Analysis and Epidemiology, NCHS

## COOPERATING UNITS (if any)

National Center for Health Statistics

## LAB/BRANCH

Biometry Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

.05

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unindented type. Do not exceed the space provided.)

The purpose of this agreement is to provide support for the 1991 Wave of the NHEFS. The NHEFS is a longitudinal study which uses as its baseline those adult persons ages 25 to 74 years of age who were examined in the NHANES I. During the period of May to July 1990, the NCHS conducted tracing procedures to keep abreast of the cohort. Upon award of a contract in 1991, the contractor will conduct a 30-minute telephone interview on eligible subjects and death certificates for newly identified deceased subjects will be obtained.

These additional years of followup will provide important outcome information on mortality and hospitalization and the added age span of the 1991 wave will provide information on individuals up to approximately 94 years of age.



### **Demography and Economics Office**

The EDB Program announced the availability of a report entitled, "The NIA Macroeconomic-Demographic Model: Alternative Futures for the Retirement Income System." This publication describes projections of future consumer expenditures on health care and other goods and services under alternative scenarios. The projections are based on simulations performed with a large-scale macroeconomic-demographic model of the nation's retirement income system developed by Lewin/ICF, Incorporated under contract (N01-AG-5-2106) with EDBP/NIA. Projections are made into the next century and depict the consequences of the dramatic demographic changes that the United States population will undergo.

With the departure to another Federal Agency of the Office Chief, Dr. William Cartwright, the EDB Program and its Ad Hoc Scientific Advisory Committee are evaluating future directions for this important National Institute on Aging interest area.

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## Biometry Office

The Biometry Office performs a variety of functions involving the development and application of mathematical and statistical methods for EDB Program data on the epidemiology and demography of aging and health. The Office also provides statistical consulting, computing, graphics, and data management services to the other units within EDB as well as other Programs in NIA, other NIH Institutes, other Government agencies, and the private sector.

The developmental activities and achievements of the Office are summarized below by the projects to which they apply. One personnel change took place in the Biometry Office which has affected several of the activities listed below. Donald Everett, statistician, left the Program during the year, requiring the remaining staff to assume a number of duties while his position is under recruitment. The most important duty was that of Project Officer for the Duke EPESE project. Those responsibilities have been assumed by Dr. Brock for the time being. Other responsibilities will be discussed as they appear in the listing of various projects, which are organized by major category.

### 1. Established Populations for Epidemiologic Studies of the Elderly (EPESE)

As in the past the EPESE projects were the focus of numerous Office activities in FY 1990. Mr. Foley continues as Project Officer for the New Haven site with the attendant requirements for administrative action. As mentioned above, Dr. Brock has assumed the responsibility of Project Officer for the Duke site with the departure of Mr. Everett. This comes at the time of a major contract renewal for two additional waves of data collection (Telephone Follow-up IV and In-person Follow-up III) followed by 5 additional years of surveillance for mortality and morbidity endpoints. Development of new protocols and instruments will be required to take advantage of emerging opportunities for new topics to be studied at this site commensurate with recent developments in the field and with recommendations of the EDB Scientific Advisory Committee. In addition, we anticipate requests for consideration of topics suggested by the incoming Associate Director for EDBP. Thus the administrative requirements for this project are likely to be considerable for the foreseeable future.

A second function so ably performed by Mr. Everett was that of coordinator of activities related to an Interagency Agreement with the Health Care Financing Administration (HCFA) for support of analysis of EPESE data on the use of prescription and non-prescription drugs. Again Dr. Brock has assumed these duties and has executed a modification to





the existing contract for additional drug data analysis at the Duke site. Mr. Everett executed three professional services contracts to develop recommendations of pharmacoepidemiologic analyses using EPESE data. Reports will be prepared highlighting important and needed research in this field which can be addressed with these data. Also, the staff has provided orientation materials for a new HCFA Project Officer. Mr. Foley is maintaining and enhancing strong liaison with the Office of Research and Demonstrations, HCFA. We are hopeful that this association will continue to provide a useful dialogue with the agency and be of benefit to other activities where there is common interest as well as insure that the EPESE drug data are utilized to their fullest potential.

Biometry Office staff have continued in their efforts to complete the Duke EPESE Resource Data Book, which is now ready to go to publication. Computing staff have continued their involvement in the production of the text through the use of the desktop publishing software available in the EDB Program. Mr. Everett and Dr. Brock have completed the technical appendix on methods which explains the use of the Duke complex sample survey data, carefully adjusting for the complex design of the sample and providing smoothed estimates of the sampling variances which permit correct inferences to be made from the study. The book should be available for distribution very soon.

Collaboration on the older drivers' study with the National Highway Traffic Safety Administration (NHTSA) and the two EPESE sites (Iowa and New Haven) continues in the area of analyses of 1989 interview data and the development of a database linked to record data from each site's Department of Motor Vehicles (DMV). The University of Iowa successfully linked its EPESE participants to the DMV records this past summer and are developing the database format and documentation in collaboration with NIA and Yale University. This task was facilitated by the fact that the driver's license number is the same as the Social Security Number. In New Haven, DMV data have been more difficult to obtain because the participants' license numbers are unique numbers. Connecticut's DMV will work with Yale University in determining the license numbers through a matching of personal identifiers.

Data from the 1989 EPESE survey of driving practices were presented in August at the American Statistical Association Meeting and in November at the Gerontological Society of America Annual Meeting. A manuscript describing the results of the survey is being developed by Mr. Foley and Dr. Eberhard (of NHTSA) for submission to Public Health Reports in the fall. Investigators at both sites will continue collaborating with NIA in defining more focused analyses using the health and functional performance measures from



the previous years of data to test hypotheses about morbidity and the ability to continue driving safely.

In response to the need for more epidemiologic information about the prevalence, incidence and risks for developing sleep problems (NIH Consensus Conference: Sleep Disorders of Older Persons), Mr. Foley and Dr. White have begun analyses of the EPESE data on this topic. Mr. Foley presented some of the EPESE data on sleep at the Annual Meeting of the Maryland Gerontological Association in May of 1990. Although the majority of the EPESE participants complained in one or more of the five questions about sleep, no more than 10 percent complained in two or more of the three night-time problems along with at least one of the two daytime problems (i.e., a significant sleep complaint). Baseline data on the use of medications, when grouped into therapeutic classes, were shown to be highly predictive of a significant sleep complaint. Further analyses are focused on hypotheses about the use of specific medications and the development of each complaint.

Other analyses of relevant EPESE data are underway at this time. Ms. Losonczy is collaborating with Dr. Huntley in addressing the impact of co-morbidity on mortality and disability. The study examines the degree to which hip fracture leads to increased disability and/or mortality when co-existing with hypertension. This analysis follows closely earlier analyses examining the simultaneous occurrence of more than one chronic condition in an older person. Another such collaboration between Ms. Losonczy and Dr. Huntley involves the examination of the influence of body weight on mortality in older persons using EPESE data. Results from an earlier analysis of NHANES I data were used to develop cutpoints of body mass indexes (BMI's) as reflected in that nationally representative population study. The EPESE data are now being analyzed utilizing the NHANES I cutpoints.

Two other projects involving analyses of EPESE data are worthy of mention. Mr. Foley has completed a chapter on the use of nursing homes (based to a large extent on the EPESE nursing home data) for a textbook entitled, "Methodologic Issues in the Epidemiologic Study of the Elderly," edited by Drs. Robert Wallace and Robert Woolson of the University of Iowa for the Oxford University Press. Finally, Drs. White and Brock are collaborating with Dr. Jon Lemke, also of the University of Iowa, on an analysis of EPESE data on hearing loss. The relationship of hearing loss to the use of non-steroidal anti-inflammatory drugs and tricyclic antidepressants is being examined in this analysis.



2. National Health and Nutrition Examination Survey (NHANES) and NHANES Epidemiologic Follow-up Survey (NHEFS)

Collaboration with the National Center for Health Statistics (NCHS) has continued during FY 1990. Dr. Brock has assumed responsibilities as Project Officer for this continuing Interagency Agreement. As reported last year, four Biometry Office staff have participated in the production of the book entitled "Health Status and Well Being of the Elderly", published by Oxford University Press this year. Staff contributed to chapters on physical functioning, arthritis, stroke and nutrition. In addition, separate papers on arthritis, arthritis and mortality, black-white differences in stroke, and food group consumption were completed. A paper on body weight and mortality has been submitted to the Journal of the American Medical Association.

Ms. Losonczy and Dr. White have collaborated on an analysis of the association of dietary vitamin E and age-dependent disease. In this analysis, vitamin E was examined as the primary predictive factor in looking at several chronic diseases as outcomes, while controlling for a number of independent factors, such as demographics and various health characteristics measured in the NHANES II. The hypothesis was that vitamin E would be protective against the development of certain diseases. This was borne out in this study for systolic blood pressure, emphysema and coronary heart disease for some subgroups of the population. Ms. Losonczy presented preliminary results of these analyses at the June 1990 meeting of the Association for Food and Society in Philadelphia. A draft paper has been written, summarizing the results to date, but analyses are continuing.

Interest in the relationship between nutrition and characteristics of older persons continues in other areas. Mr. Everett collaborated on analysis of data from the NHEFS on kidney disease, diet and subsequent mortality among older persons. He also participated in a consultation with the Frances Stern Nutrition Center, New England Medical Center Hospitals on the use of NHANES and NHEFS data. In addition, Ms. Losonczy attended a meeting on Nutrition Research: Future Directions and Applications at Duke University in March of 1990, and the annual meeting of the National Association of Clinical Nutrition in Washington in May of this year.

3. Survey of the Last Days of Life

Analytic and writing activities have continued for this descriptive study of older decedents in Fairfield County, Connecticut. Dr. Brock completed a chapter for the Wallace

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and Woolson text (Oxford University Press - see above) which provides a comprehensive discussion of the methodological issues and problems faced in the design and conduct of this study. The book is due to be published later this year. Previously-reported analyses on health status trends in the last year of life and transitions among residential and care settings in the last 3 months of life are being refined for submission of final results for publication later this year.

Dr. Brock and Mr. Foley have collaborated on a paper which examines the use of telephone interviews in the course of conduct of the last days of life study. Because of the occasional difficulty of locating the next-of-kin of the decedent or another person appropriate to interview about the decedent, it was sometimes necessary to conduct interviews by telephone. In addition, some informants for this survey were reluctant to be interviewed in person, either because of their busy work schedules (in the case of some offspring of the decedents) or because of the fear of having a stranger enter their homes (in the case of older widows especially). Thus, in order to maximize the response rate for the study, the protocol allowed telephone interviews in these types of cases as well. The analysis was done to examine the quality of the telephone interview data as compared to the in-person interview data. Results showed very similar response patterns for the two modes of survey, and the amount of missing data for the survey was not significantly influenced by the use of the telephone. These results were presented at the annual meeting of the American Statistical Association in Anaheim, California.

Dr. White, Ms. Losonczy and Dr. Brock are collaborating on a paper to examine data from this study on the mental status of the decedents as measured by several questions which were included in the interview. Specifically, the respondent was asked if the decedent had ever been diagnosed clinically with Alzheimer's disease or other dementia, and whether the decedent was aware of his/her surroundings or who was present, the day before death, a typical day one month before death, and a typical day one year before death. The responses to these questions and results on activities of daily living have led us to construct an index of functioning which may be useful for describing cognitive impairment among these decedents and studying the association of dementia, cognitive impairment and physical functioning with lifetime histories of stroke, Parkinson's disease and hip fracture among other conditions. This analysis is continuing.

Dr. Brock is collaborating with Dr. Hans Kaiser of the University of Maryland on an analysis of data for the 260 decedents with an underlying cause of death of cancer in the last days of life study. The paper is descriptive and





focuses on issues related to symptoms and functioning in the last days of life. Preliminary results will be presented at the Third Annual International Consensus on Supportive Care in Oncology in Brussels, Belgium.

#### 4. Data Management and Statistical Computing

The computing staff is continuing with the sizable effort put forth in conducting final editing of several of the EPESE data sets, in particular the baseline and second in-person (follow-up III) interview data sets. In attempting to expedite this activity, the EDB staff has provided the data collection centers with editing programs which have been used by EDB in previous reviews of the data received from the sites. In addition, Ms. Lafferty and Ms. Phillips have made recent visits to the three sites involved in this data cleanup activity, with very good results from each visit. More rapid progress is now being made with the expectation that the cleanup of the telephone follow-up files will proceed much more quickly than those for the in-person files, and it is likely that a clean file for the third in-person interview will be completed for all three sites this year as well.

Work is once again proceeding on the computer support services contract solicitation after a delay of some time caused by a shortage of staff in the NIH Division of Procurement. The schedule now calls for a start date sometime in the Fall of this year. This contract is crucial to the Program's ability to maintain its momentum in data analytic activities with the arrival of new staff members in the Epidemiology Office. One of the primary purposes of the contract is to provide data analytic support for epidemiologists conducting analysis of EPESE and other data. In addition, support will be provided for installation, maintenance and evaluation of new software and hardware and some of the editing and documentation requirements for public release of the EPESE data. Also, we will be asking the Contractor to assist our programming staff in investigating other computing needs of the Program as they arise.

Ms. Lafferty has executed a professional services contract with NETCOMM to provide additional enhancements to the local area network available to the Program. This has resulted in a number of improvements in service available to staff and additional communications availability not only with other Programs at NIH, but with outside organizations, particularly through the BITNET system.

Ms. Lafferty has extended work on a PC-based system for analyzing EPESE data known as the CD-WORM (compact disk-write once read many) system under a professional services contract with the University of Texas Health Science Center



at Houston. The prototype system, known as UTMOST, was created last year to include EPESE baseline and mortality files for one site. The system is now being extended to include not only data from other sites but also data from other collection waves of the EPESE, so that eventually all data sets will be available for analysis through this system. Tests of the prototype have shown that the system is capable of allowing ready access to EPESE data for analysis that is both timely and cost effective.

The production of high-quality computer graphics continues as in the past, with Biometry Office staff providing quick turnaround for publications and presentations. Dedicated equipment and a dedicated staff make this system work very well. The new desktop publishing software was extremely valuable in the production of the Duke EPESE Resource Data Book.

As in the past the computing staff continues to provide valuable service to the Program in analytic support, maintenance of computing equipment, installation of hardware and software and consultation on computing problems. Katie Wilkins, a summer student working in the Program this year, has been quite helpful in a number of these activities as well as in providing computing support for data analysis.

#### 5. Statistical Methodology Activities

A meeting of EPESE project statisticians was held on March 1, 1990, to discuss in detail the effects of missing data on analysis of EPESE data. Dr. Lemke of the Iowa site made a 2 hour presentation of results of investigations which had been ongoing at Iowa and NIA regarding methods for dealing with missing data. A discussion ensued during which the following recommendations were made: 1) for analyses with missing covariates, use of indicator variables for missing data was suggested; 2) multiple imputation is an acceptable methodology when the outcome variable is missing; 3) the E-M algorithm, although computationally intensive, is also useful for dealing with missing data. Finally, the group stated that although it was not practical to implement a blanket policy on handling missing data in the EPESE, it is important for all sites to be aware of the problem and to determine to the extent possible why data are missing.

Further investigations into ways to handle missing data in the EPESE are continuing. It is anticipated that a manuscript outlining the results to date will be forthcoming.

A contract based on 1 percent departmental evaluation funds was awarded to Dr. Laurel Smith of Harvard University to conduct an evaluation of existing and emerging statistical methods for analysis of longitudinal data from epidemiologic



studies, especially measures of physical functioning from the EPESE. The Contractor has thus far conducted a search of the statistical literature on the subject, documented the theoretical properties of a number of statistical techniques, and fitted some of those models to several years' data on functioning from the EPESE locations in East Boston and Iowa. The results so far indicate that random effects linear models adequately describe the observed patterns of change in functioning, with several other techniques still to be evaluated. One of the difficulties encountered in this study is the availability of documented computer software for some of the analyses. At the end of the year, we will receive from the Contractor a complete report discussing all the findings and making recommendations for implementation of the techniques determined to be most appropriate for use with our data. We attach great value to the findings from this study which we anticipate will transfer to analyses of many other data sets involving longitudinal change in the EPESE.

In preparing the design for the Women's Aging Study (WAS), a request was made to provide estimates of minimum sample sizes required to detect differences in development of disabilities over time in this prospective study. It was possible to utilize some of the data available from the EPESE to establish a cohort of disabled persons from which the measures of variability could be obtained to complete the calculations. Sample sizes could be estimated for studying differences in outcomes as a function of single risk factors one at a time. In fact, it would be possible to derive such estimates as a function of several risk factors, given the richness of the EPESE data. However, accounting for the simultaneous effects of all the risk factors would require the joint probability distribution of all the risk factors and the variance-covariance matrix under the null and alternative hypotheses as well as the multiple correlation relating the first (or most important) risk factor to all the others. The details of such a procedure have been worked out only for the case in which all the risk factors follow a multivariate normal probability distribution. Our data include a mixture of discrete and continuous variables, and the current literature offers no immediate solution. Thus additional effort would be required to carry the project to completion in its full detail. We anticipate continuation of this activity into the next year.

The project reported last year involving development of new software for the analysis of complex sample survey data has continued. The Contractor has completed a revised version of the first phase of the software which incorporates all the required modifications to the previous versions. The second phase of the project is now underway, leading to the development of programs for more sophisticated analytic



techniques, particularly in the areas of generalized linear models, categorical data analysis, logistic regression and proportional hazards models. All of these techniques will be extremely useful to EDB analysts' use with data from the NHANES, other NCHS surveys, and the New Haven and Duke EPESE. The program is known as SUDAAN.

6. Consultations and Collaborative Analyses Utilizing Other Data Sources

Planning has begun for the next cycle of the National Mortality Followback Survey to be conducted in 1992 by the National Center for Health Statistics. The EDB Program helped sponsor the previous cycle in 1986 through an Interagency Agreement to support additional questions on cognitive functioning and the use of nursing homes by the decedents whose next-of-kin were surveyed in this study. We have found the information gathered in that study to be valuable in providing national baseline statistics on those characteristics for comparison with similar data from the community-level survey of the last days of life. It is important to be able to document change in those characteristics by collecting additional data at a second point in time. This is especially true for the data on cognitive function in view of the changing perception on the part of the public in recognizing cognitive deficits in the older population. Also, additional data on health care utilization will assist in determining whether there is increased public awareness of the availability of home care services as an alternative to nursing homes as a source of long-term care. The survey will permit national estimates of these items in the presence of knowledge about causes of death, lifestyle factors, use of other types of services and other information from the death certificate. Finally, this survey affords us a rare opportunity to study health characteristics of centenarians in the period immediately before death in a way not previously possible. With population data available from the 1990 Census, we can estimate the number of centenarians likely to be included in the sample and design strategies to oversample them for the survey. Planning for this operation will be continuing.

Mr. Everett continued to serve as a consultant to National Institute of Arthritis and Musculoskeletal and Skin Disease and the Indian Health Service on a collaborative study of the epidemiology of the spondyloarthropathies in Native Alaskan populations. Work continued on estimating the prevalence of these conditions, and investigation of the potential influence of genetic and environmental factors in the pathogenesis and expression of these disorders.

Dr. Brock participated in a National Cancer Institute conference on access to care for cancer patients. Some of the data from the last days of life study were shared in the

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discussions. Also, Dr. White and Dr. Brock attended a National Academy of Sciences conference on epidemiologic studies in military and veteran populations. Of primary interest in this meeting was a discussion of a study of dementia among twins, funded by a grant from NIA.

Dr. Brock served as a statistical consultant to the Health Care Financing Administration on the development of the design and analytic plans for the upcoming Medicare Current Beneficiary Survey. This survey is being done to collect data on the use of medical services by Medicare beneficiaries and the costs and sources of payment. Of interest from a methodological point of view is the requirement by HCFA for the data collection to be done by computer assisted personal interviews (CAPI), in which interviewers take laptop computers into the homes of the respondents and conduct the interviews and data entry operations on site. It is believed that this is one of the first application of this technology in a large-scale, nationally representative sample.

Dr. Brock has served the local statistical community by assuming a position as representative-at-large on the Board of Directors of the Washington Statistical Society (WSS). In this position, he has helped to organize a WSS Quantitative Literacy initiative for the Washington metropolitan area which involves organizing volunteers to provide a variety of statistical expertise to Washington area school systems. He also served the national organization, the American Statistical Association, as chairman of the George W. Snedecor Award Committee, which recognizes each year the best published paper in biometry.

## 7. Research Highlights for Fiscal Year 1990

- Data on osteoarthritis of the knee from the NHEFS do not support an association between the presence of pain at baseline and subsequent mortality, but do predict symptoms at follow-up. Specifically, logistic regression with adjustment for age showed statistically significant differences in the frequency of knee pain at NHEFS when those who initially had normal radiographs and no symptoms were compared to three other groups: those with symptoms but no radiographic changes, those with no symptoms but positive radiographs, and those who had both symptoms and radiographic findings. Similarly, persons who reported knee pain at baseline or had radiographic findings at baseline but both were significantly more likely to have had difficulty walking when compared to those who were free of symptoms or findings at baseline. Thus, pain and radiographic abnormalities of the knee are strongly predictive of disability for weight-bearing activities a decade later. (Lawrence et al., Arthritis, in Cornoni-Huntley, Huntley and



Feldman, eds. Health Status and Well-Being of the Elderly, Oxford University Press, 1990, pp.136-151.)

- Data on dietary patterns in the elderly were presented from the NHEFS. Analysis showed that the mean number of servings of the meat group exceeded the recommended two daily servings, that the number of servings of milk and bread was lower than recommended, and that the number of servings of fruits and vegetables was also low if the question on intakes of all fruits and vegetables was used in the analysis, but exceeded the recommendation if servings of 41 individual items were added together. Changes in health status and changes in food group servings showed several relevant differences among those who were diagnosed as diabetic or as having diverticulitis. Data from this study support the conclusion that there is no clear evidence that overeating is associated with obesity and that obese older persons tend to report fewer total servings and tend to choose less calorically dense foods than normal or underweight persons. (Murphy et al., Dietary patterns, in Cornoni-Huntley, Huntley and Feldman, eds. Health Status and Well-Being of the Elderly, Oxford University Press, 1990, pp. 184-209.)

- Data on the assessment of physical functioning was available only cross-sectionally in the NHEFS, since no functioning measures were obtained at baseline. However, logistic models were fitted to explain associations between certain baseline characteristics and poor functioning at follow-up as well as mortality at follow-up. Men who participated in one or more of the baseline arthritis and cardiovascular/respiratory supplemental data collections (based on reported symptoms at baseline) were significantly more likely to have functional disability at follow-up, and those participating in the cardiovascular/respiratory supplement were more likely to have died. For women the results were the same for disability, but only those women who participated in more than one supplement were at increased risk of mortality. Another analysis examined associations between baseline measures of four health perceptions and behaviors. For men the mortality risk was about 50 percent higher for those with fair or poor perceived health compared to those with good or excellent health. Similarly, the mortality risk was 50 percent higher for those with little or no exercise than men reporting moderate or much exercise. Men who smoked had an 80 percent increased risk of dying, but former smokers showed no greater risk of mortality. Among women, the corresponding odds ratio for fair or poor health was 1.5, for current smokers 1.6 and for former smokers 1.8. (Foley et al., Physical function, in Cornoni-Huntley, Huntley and Feldman, eds. Health Status and Well-Being of the Elderly, Oxford University Press, 1990, pp. 221-236.)



- Analysis of the latest available data on the demography of aging from the Census Bureau, the National Center for Health Statistics and the EDB Program showed continuing declines in overall mortality for the older population and rapid growth of the population age 85 and older. Projections of the older population into the twenty-first century indicate ever-increasing numbers of very old persons with declining function and increased use of health services. (Brock, et al. Demography and epidemiology of Aging in the United States, in Schneider and Rowe, eds. Handbook of the Biology of Aging, Third Edition, Academic Press, 1990, pp. 3-23.)

- Descriptive data from the North Carolina EPESE showed a median age of 71.6 years for the cohort, with most of the age variation among subgroups of the population being between men and women. While most black men were married (65.1 percent), the majority of black women were widowed (54.9 percent). Among whites the corresponding percentages were 83.6 for married men and 53.1 percent for widowed women. Income levels for these persons were generally under \$10,000 per year, and most had lifetime occupations in the "blue collar" categories. While less than one-fifth of the respondents reported being currently employed, about three-fourths reported being retired from at least one job. (Brock, et al. Demographic characteristics, in Cornoni-Huntley et al., eds. Established Populations for Epidemiologic Studies of the Elderly: Resource Data Book, Volume II, NIH Publication No.90-495, 1990.)

- Analysis of descriptive data on physical functioning from the North Carolina EPESE showed that for each activity of daily living, the majority of participants (90 percent) reported no difficulty in completing the task. The percentages were quite similar to those reported at the other three EPESE sites. As in the other sites men reported higher rates of independence than did women. For gross mobility activities rates of dependence were higher, averaging in excess of 20 percent overall, once again with women reporting higher rates of disability. White men were more likely to report the use of a hearing aid than black men (5 percent compared to less than 1 percent), whereas the comparable percentages were smaller for women (2 percent for whites versus less than 1 percent for blacks). An estimated 79 percent of black men compared to 93 percent of white men reported use of eyeglasses and/or contact lenses. Among women the comparable percentages were 93 for blacks and 97 for whites. (Foley et al., in Cornoni-Huntley et al., eds. Established Populations for Epidemiologic Studies of the Elderly: Resource Data Book, Volume II, NIH Publication No. 90-495, 1990.)

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